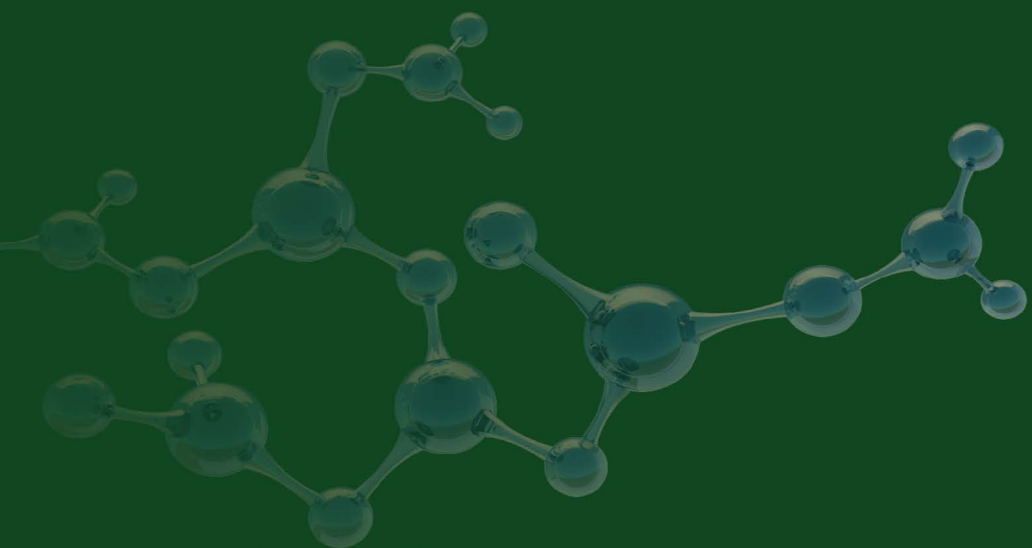
Neuro-Nutraceuticals and Drug Discovery and Delivery in Alzheimer's Disease

Volume 2

Strategies to Unlock the Brain's Fortress



Varinder Singh
Amit Kumar
Parul Sood
Editors

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NEURO-NUTRACEUTICALS AND DRUG DISCOVERY AND DELIVERY IN ALZHEIMER'S DISEASE

Volume 2

Strategies to Unlock the Brain's Fortress

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Strategies to Unlock the Brain's Fortress

Varinder Singh, PhD
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Dedication

This book is dedicated to
God Almighty and our parents.

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Preface

Welcome to *Neuro-Nutraceuticals and Drug Discovery and Delivery in Alzheimer's Disease, Volume 2: Strategies to Unlock the Brain's Fortress,* a comprehensive exploration into the cutting-edge strategies aimed at unlocking the brain's fortress in the pursuit of effective Alzheimer's management. This book delves deep into the synergistic domains of nutraceuticals and advanced delivery methods, offering a nuanced perspective on the multifaceted approach required to tackle the challenges posed by Alzheimer's disease. In this book, we delve into two crucial sections, each contributing uniquely to our understanding and potential interventions in the relentless battle against Alzheimer's.

The first section of this book is dedicated to a holistic exploration of nutraceuticals and their pivotal role in managing Alzheimer's disease. As our understanding of the intricate relationship between nutrition and brain health deepens, myriad nutraceuticals emerge as potential allies in the fight against cognitive decline. This section serves as a guide to the diverse array of neuro-nutraceuticals, providing insights into their mechanisms, efficacy, and potential integration into holistic Alzheimer's management strategies.

Unlocking the secrets of the brain's fortress requires innovative strategies for delivering therapeutic agents effectively across the blood-brain barrier. The second section of this book focuses on the recent developments and advancements in the delivery of nutraceuticals, exploring novel techniques and technologies that aim to breach the formidable barrier guarding the brain. From nanotechnology to advanced drug delivery systems, this section examines the forefront of research dedicated to enhancing the bioavailability of nutraceuticals in the brain, thereby opening new avenues for therapeutic interventions in Alzheimer's disease.

As editors of this volume, we are thrilled to present a collection of chapters that not only reflect the current state of knowledge but also pave the way for future exploration in the field. The collective expertise of our esteemed contributors, spanning diverse disciplines, ensures a rich tapestry of insights that will appeal to researchers, clinicians, and students alike.

In navigating the pages of this book, we encourage readers to engage with the evolving landscape of neuro-nutraceuticals and advanced delivery strategies. The journey through these sections promises to be both enlightening

and inspiring, offering a glimpse into the exciting possibilities that lie ahead in the quest to unravel the mysteries of Alzheimer's disease.

—***Editors***

PART I

Nutraceuticals: Holistic Approaches to Alzheimer's Management

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CHAPTER 1

Emergent Natural Antioxidant Therapeutics to Cope with Oxidative Stress in Alzheimer's Disease

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ABSTRACT

A significant pathophysiological alteration in Alzheimer's disease (AD) is oxidative stress. By causing mitochondrial malfunction, boosting metal toxicity, and creating vicious pathophysiological cycles, it is intimately related to amyloid pathology and tau pathology. Thus, oxidative stress, which is an important pathogenic indicator of AD, can be a target for therapy. Antioxidants are the body's defense system, targeting reactive oxygen species and thus reducing oxidative stress. Antioxidants can be produced endogenously in the body or obtained exogenously through the diet from natural sources such as fruits and vegetables. The natural sources of these antioxidants exhibit a beneficial effect on health via the phytochemicals contained in them that exert antioxidant properties. The phytochemicals are non-enzymatic in nature and include organosulfur compounds, terpenoids, and polyphenols. These are widely distributed in foods such as fruit, vegetables, tea, and traditional medicinal herbs. The connection between oxidative stress and AD pathogenesis as well as the neuroprotective function of natural antioxidants derived from natural sources are addressed in this review.

Neuro-Nutraceuticals and Drug Discovery and Delivery in Alzheimer's Disease, Volume 2: Strategies to Unlock the Brain's Fortress. Varinder Singh, Amit Kumar, Parul Sood (Eds.)
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Furthermore, the therapeutic potential of natural antioxidants as AD treatments and/or prevention measures is explored.

1.1 INTRODUCTION

The primary cause of dementia is Alzheimer's disease (AD), which is becoming more prevalent, affecting millions of individuals worldwide. The cause of the sporadic disease has not been identified; however, environmental, genetic, sex, and age factors play a crucial role in the onset of the disease, whereas familial cases are much less common and are caused by mutations in genes coding for amyloid-β protein precursor and genes encoding for presenilin 1 and presenilin 2, which participate in the processing of the amyloid-β protein precursor. The pathological feature that marks the presence of the disease is the extracellular cortical build-up of amyloid plaques and neurofibrillary tangles inside cells. The α-secretase catalyzes the cleavage of Amyloid-β protein precursor in the plasma membrane, whereas the β- and γ-secretases catalyze the cleavage such that there is an extracellular release of amyloid-β peptide, which is prone to agglomeration and plaque formation. Since the trans-Golgi network, endoplasmic reticulum, lysosomal, and mitochondrial membranes all contain the amyloid beta precursor protein, the Amyloid-β peptide may have been produced within the cell, resulting in intracellular plaque deposition. Another hallmark of the molecular mechanisms involved in AD pathology is the intracellular deposition of neurofibrillary tangles. Tau is a protein that aids in the stabilization of microtubules and neuronal trafficking signals. In AD, tau gets hyperphosphorylated, resulting in its dissociation from microtubules and the disruption of trafficking signals in neurons. This hyperphosphorylated tau protein forms further intracellular aggregates. When brain imaging scans of AD patients reveal the presence of the above pathological features, a diagnosis of AD could be made [1, 2].

1.2 AD AND OXIDATIVE STRESS

In some people, the accumulation of the amyloid-β peptide did not lead to the onset of cognitive symptoms, indicating that different processes may be at play in the etiology of AD [1]. A significant pathophysiological alteration in AD is oxidative stress. Oxidative stress participates in the development of AD by causing mitochondrial malfunction, boosting metal toxicity, and creating vicious pathophysiological cycles that are intimately related to Aβ peptide and tau protein accumulation. An important pathogenic indicator of AD, oxidative stress can also be a target for therapy [3].

In normal cellular pathology, a balance exists between reactive oxygen species (ROS) levels and antioxidant enzymes. Whereas in AD, there is an increase in production of ROS along with alterations in the antioxidant enzymes which result in oxidative stress. Oxidative stress markers include: increased level of glycosylated products and of oxidized proteins; extensive lipid peroxidation; the formation of alcohols, aldehydes, free carbonyls, ketones, and cholestenone. Alzheimer's disease is marked by disruption of oxidative phosphorylation in the mitochondria of hippocampal neurons and subsequent mitochondrial dysfunction which leads to overproduction of ROS. In sporadic disease, mitochondrial dysfunction can be caused by aging, and in other cases, we can say that mitochondrial dysfunction is a hallmark of the disease's pathology. Mitochondrial ROS could cause mitochondrial membrane potential to decrease, thereby further increasing ROS production inside the same organelle [1]. As a response to increased ROS, Aβ, when present in lesser concentrations, confers neuroprotection by preventing oxidative damage caused by the elevated ROS level-induced auto-oxidation of lipoproteins present in the plasma and CSF. Therefore, oxidative stress and Aβ peptide concentration are initially inversely related, and it seems that Aβ is produced initially to protect neurons from such oxidative damage. However, after a certain point, the concentration of Aβ peptide increases with an increase in ROS levels, because an increase in ROS levels alters the activity of α-secretase and increases the activity of β- and γ-secretases. This leads to an increased rate of Aβ peptide formation and agglomeration. This large amount of Aβ agglomerates causes even more ROS-associated damage. The damage caused by the elevation of ROS is mediated by the N-terminal kinase pathway. Furthermore, it has been observed that oxidative stress has also been linked to the tau pathology in AD. Oxidative stress causes increased oxidation of fats, which contributes to the hyperphosphorylation of the tau proteins. Additionally, there is a reduction in the activity of superoxide dismutase (SOD1 and SOD2) and an increase in the activity of p-38 mitogen-activated protein kinase, which leads to hyperphosphorylation of tau protein and its dislocation and destabilization of microtubules, thus causing neuronal damage [3].

1.3 ROLE OF NATURAL ANTIOXIDANTS USED IN AD

Increased oxidative stress could lead to damage at the cellular level. To combat such damage, antioxidants are produced. Antioxidants confer protection against such damage by scavenging these free radicals or by reacting with them

to produce a less reactive product. Antioxidants can be sourced from natural or synthetic origins, and they can be enzymatic or non-enzymatic in nature. Superoxide dismutase (SOD), Glutathione peroxidase (GPx), and catalase are classified as enzymatic antioxidants and are produced endogenously. Antioxidant capacity of the body is determined by the availability of such enzymes, whereas vitamins A, C, E, and D, co-factor Q10, and various minerals (zinc, selenium) are classified as non-enzymatic antioxidants and are available from exogenous sources, i.e., through diet (Figure 1.1). Natural antioxidants are classified into non-enzymatic and enzymatic antioxidants. Non-enzymatic antioxidants can be obtained through diet whereas enzymatic antioxidants are produced endogenously in our bodies. Numerous clinical studies conducted for different natural antioxidants in AD are given in Table 1.1.

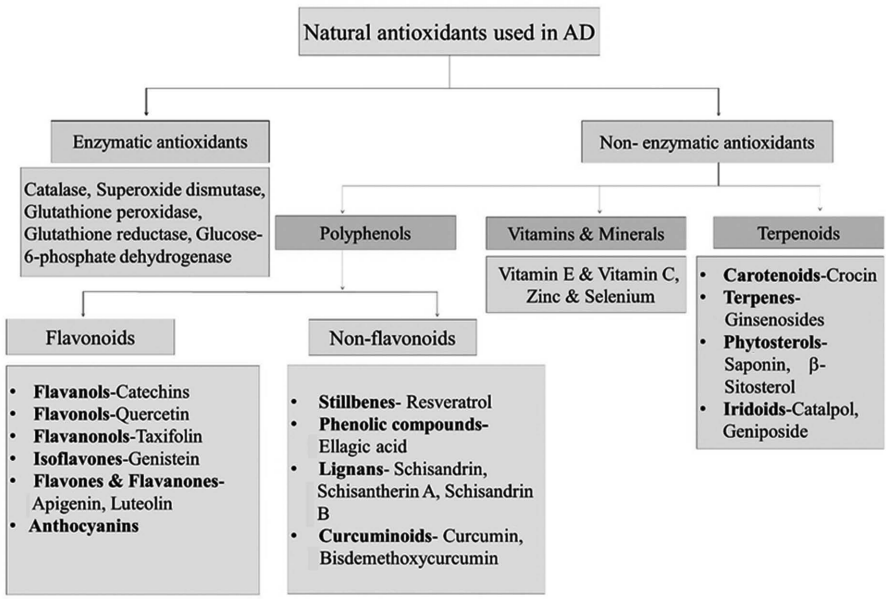

FIGURE 1.1 Classification of natural antioxidants.

1.3.1 ENZYMATIC ANTIOXIDANTS

There are different types of primary antioxidant enzymes present, like SOD, catalase, and GPx, and secondary antioxidant enzymes like glutathione reductase and glucose-6-phosphate dehydrogenase (G6PDH). The superoxide radical is generated through mitochondrial oxidative phosphorylation inside the mitochondria. This superoxide free radical then reacts with

TABLE 1.1 Clinical Studies Conducted for Natural Antioxidant Relevant to AD

Compound	Participants	Intervention	Primary Outcome	Main Result	References
Epigallocatechin-3-gallate	87 participants with DS neurological disease.	9 mg/kg daily orally of EGCG for 12 months.	Variation of cognitive function and in amyloidosis biomarkers.	When compared to placebo, EGCG for a full year improved inhibitory control, adaptive behavior and visual recognition memory.	NCT01699711
Quercetin	12 participants with AD.	Nutritional supplement containing optimized quercetin daily for 6 weeks followed by 12 weeks with or without etanercept.	Difference in the treatment outcome when given with etanercept and without on mini-mental status examination (MMSE) score.	Results not published.	NCT01716637
Genistein	72 participants with AD.	100 mg/day of soy isoflavones.	Difference in cognitive outcomes such as language, executive function and memory.	Association between plasma equal levels and verbal fluency and speeded dexterity, No discernible effects on cognition.	NCT00205179 [67]
Genistein	27 participants, aged 18 and up, with AD.	60 mg of genistein b.i.d. for 360 days.	Changes in the concentration of amyloid beta in CSF.	Improvement in the complutense verbal learning test (TAVEC) and Rey complex figure test, decreased uptake of Aβ in the anterior cingulate gyrus.	NCT01982578
Anthocyanin	31 subjects with poor cognitive functions as assessed by Rey auditor verbal learning test.	500 ml of tropical juice for 3 times/day and 3 days/week for 10 weeks. Where juice contains 9,135 mg of GAE and 194.1 mg of cyanidin-3-glucoside of total anthocyanin.	Attenuation of cognitive function, oxidative stress and metabolomics profiles.	Improvement in Rey auditory verbal learning test (RAVLT) and comprehensive trail making test (CTMT), increased urinary excretion of thyroxine and 3-methyadenine.	[68]

TABLE 1.1 *(Continued)*

Compound	Participants	Intervention	Primary Outcome	Main Result	References
Resveratrol	119 participants aged 50 years and older with AD.	500 mg once daily, increased at 13 weeks to 1 g PO twice daily as 500 mg capsule.	Changes in volumetric magnetic resonance imaging (MRI) and in biomarker analysis.	Attenuated ADL (ADSC-ADL) scores, MMSE scores and decline in Aβ42 levels. Reduced CSF MMP9, increased interleukin (IL)-4, macrophage-derived chemokine (MDC), fibroblast growth factor (FGF)-2).	NCT01504854 [69]
Lignans	21 participants with MCI.	One AS capsule (containing 3 mg of astaxanthin and 5 mg of sesamin) and one placebo capsule every day for 12 weeks.	Impact on cognitive functions.	Central nervous system vital signs (CNSVS) test revealed improvement in processing and psychomotor speed.	[70]
Curcumin	36 participants with mild to moderate AD.	2 g/day or 4 g/day of oral curcumin for 24 weeks.	Clinical laboratory tests changes, incidence of adverse effects and AD assessment scale-cognitive subscale (ADAS-Cog).	No difference	NCT00164749 [71]
Curcumin	36 participants with gradual decline in memory and cognitive functioning for 6 months.	1 g/day or 4 g/day as powder or capsule with food and 120 mg/day of gingko leaf extract.	Variation in the level of isoprostane in the plasma and Aβ level in serum.	Results not published.	NCT00164749
Vitamin C and vitamin E	78 participants with AD.	800 IU/day of vitamin E + 900 mg/day of α-lipoic acid+ 500 mg/day of vitamin C given three times/day with meals.	Impact on oxidative damage-related biomarkers in the cerebrospinal fluid.	Reduction of the oxidative stress biomarker F2 isoprostane in the CSF.	[72]

TABLE 1.1 *(Continued)*

Compound	Participants	Intervention	Primary Outcome	Main Result	References
Vitamin E	341 patients	2,000 IU/day of vitamin E or 10 mg/day of selegiline or both selegiline and vitamin E FOR 2 years.	The onset of severe dementia or the loss of the ability to perform daily tasks.	The mini mental status examination (MMSE) score was lower, delays in the onset of primary outcomes were reported in treatment group.	[73]
Zinc	60 participants with mild to moderate AD.	Gastro-retentive zinc cysteine tablet orally once daily for 6 months with water (zinthionein).	Estimation of serum bio-metal levels by atomic absorption spectrometry.	Unknown	NCT01099332
Selenium	7,450 participants	400 IU daily of vitamin E and 200 mcg daily of selenium or 400 IU daily of vitamin E or 200 mcg daily of selenium or placebo.	Incidence of dementia (including AD).	Neither supplement prevented dementia.	NCT00040378 [74]
Carotenoids	173 healthy individuals.	1 g fish oil, 22 mg carotenoids (10 mg meso-zeaxanthin, 2 mg zeaxanthin, 10 mg lutein) and 15 mg vitamin E or placebo for 24 months.	Cognitive performance of older adults.	Improvement in working memory, reduction in dementia risk and cognitive decline later in life.	[75]
Terpenes-ginseng SG-135 (SG powder capsule, Ginseng Science Inc., Korea).	40 participants with AD.	1.5 g/day, 3 g/day and 4.5 g/day for 24 weeks.	Alzheimer's disease assessment scale (ADAS) and mini-mental state examination (MMSE) were assessed.	Improvement in ADAS and MMSE in treatment group within 12 weeks which sustained for 24 weeks.	[76]
Phytosterol	96 participants, 67 patients with AD.	Measurement of plant sterol concentration in CSF and plasma of AD patients.	Concentration of plant sterol measured by applying mass spectrometry analysis or gas chromatography.	Significantly lower concentration of brassicasterol and sitosterol in CSF of patients with AD indicating brassicasterol as a potential biomarker in AD.	[77]

bilirubin or SOD, leading to the generation of hydrogen peroxide. There are different variants of SOD, such as cytosolic superoxide dismutase (SOD1 or Cu-Zn SOD1), mitochondrial superoxide dismutase (SOD2 or Mn SOD2), and extracellular superoxide dismutase (SOD3).

This hydrogen peroxide is converted into water and oxygen molecules through enzymatic antioxidants like GPx and catalase, and through non-enzymatic antioxidants like ascorbic acid or uric acid generated via glutathione. GPx is a category of selenocysteine-containing enzymes, mostly present inside the cytoplasm, that use glutathione as a co-substrate (GSH) and convert hydrogen peroxide into water and oxidized glutathione (GSSH). GSSH is converted back into GSH via nicotinamide adenine dinucleotide phosphate (NADPH). Secondary antioxidant enzymes like glutathione reductase are involved in the generation of GSSH via NADPH, while G6PDH is involved in NADPH generation. Hydrogen peroxide, by reacting with free iron and copper, leads to the generation of a hydroxyl radical. However, some of the iron and copper may get sequestered into ferritin, transferrin, or ceruloplasmin. The sequestration of iron into transferrin is dependent upon the oxidant activity of ceruloplasmin, thus affecting its availability to participate in the Fenton reaction. That is how we can say that the activity of transferrin and ceruloplasmin undermines the availability of free iron and copper species. The superoxide radical, hydroxyl radical, and hydrogen peroxide could react with membrane lipids and nucleic acids, leading to their oxidation and damage [4, 5].

1.3.2 NON-ENZYMATIC ANTIOXIDANTS

1.3.2.1 VITAMINS AND MINERALS

There are various types of non-enzymatic antioxidants like vitamins, minerals, terpenoids, and polyphenols. Vitamins are required to perform various functions in the body and to maintain human health and metabolism. Vitamins are not produced by the body and must therefore be obtained from external sources, such as diet. Vitamins are classified based upon their solubility into two types: fat-soluble vitamins, which are soluble in fat prior to their absorption into the bloodstream, and which include vitamins A, D, K, and E; and water-soluble vitamins, including vitamin C and the vitamin B complex, which are dissolved in water [5].

Among other vitamin supplements, the use of vitamin C and E supplements has been linked to a decline in the incidence and prevalence of AD

due to their antioxidant potential. Vitamin C is a water-soluble vitamin and an important co-factor involved in various enzymatic reactions. In most mammalian species, vitamin C is produced from glucose, excluding humans, guinea pigs, and non-human primates, due to the absence of l-gulonolactone oxidase activity, which is required for the final step in the production of ascorbate. Vitamin C has been found to exert antioxidant activity by donating two of its electrons and thus preventing the oxidation of other species. After the loss of one electron, it is converted into semidehydroascorbate or an ascorbyl radical, which is less reactive than free radicals and exhibits free radical scavenging potential, and is converted into dehydroascorbate following the loss of another electron. This dehydroascorbate is either recycled back to ascorbate or is metabolized following its hydrolysis [6, 7]. Ascorbic acid, or vitamin C, has been found to inhibit telomere attrition, oxidative stress, the formation of inflammatory factors, and the disorganization of chromatin. Although *in vivo* studies have shown that vitamin C supplementation can help with Alzheimer's symptoms, human studies have yielded mixed results. Vitamin C levels have been found to be reduced in AD patients. Oral treatment with vitamin C at a dose of 50 mg/kg/day has been found to reduce oxidative stress and pro-inflammatory cytokine release induced by Aβ injection in the CA1 region of the hippocampus of the rat's brain. In another study, it was found that pretreatment with vitamin C supplementation at a concentration as low as 50–100 μM which produces intracellular concentration of 5 mM in the cells resulted in inhibition of apoptotic cell death due to Aβ in cultured SH-SY5Y neuroblastoma cells [8–10]. Besides exerting antioxidant activity, vitamin C has been found to be neuroprotective due to its ability to suppress pro-inflammatory genes and, thus, tend to modulate neuroinflammation; moreover, it causes chelation of iron, zinc, and copper and exerts an inhibitory effect on amyloid beta fibrillogenesis [8]. Current commercial vitamin C preparations include Limcee chewable tablet, zinga vita VITAMIN C AMLA EXTRACT 1,000 mg, FAST&UP Charge.

Vitamin E is a fat-soluble vitamin and includes eight homologues with potent antioxidant potential. These eight homologues are classified under two major subclasses, namely, tocopherol and tocotrienol, among which there are alpha, beta, gamma, and delta isoforms. Different variants have different biological activities. However, they commonly exhibit an antioxidant effect. The presence of a hydroxyl group on the aromatic ring of tocochromanols causes the antioxidant effect, which has

free radical scavenging properties after hydrogen atom donation. Alpha-tocopherol is the most commonly supplemented vitamin E variant. The recommended dose of alpha-tocopherol is 15 mg/day, which can exceed 1,000 mg/day. The relationship between vitamin E levels in the blood and the development of AD was investigated in several prospective cohort studies. Individuals with a higher amount of vitamin E variants in the plasma had a lower risk of developing AD in one such prospective study, conducted in a population of 232 individuals aged 80 years or older from the Kungsholmen project with a six-year follow-up. Furthermore, in a separate study of 633 people with a 4.5-year follow-up, the correlation between dietary intake of vitamin E and AD was investigated, and it was discovered that none of the 27 patients receiving vitamin E through supplementation or diet developed AD compared to the control group [11]. The commercially accessible forms of vitamin E include Evion-200 mg, 400 mg, 600 mg capsules, Evion Forte, Natvie 400 capsule, Mednovit tablets.

Zinc is a necessary element for brain function. Zinc is used for stabilizing protein structure, and it carries out catalysis of various enzymatic reactions within the body. Zinc exerts antioxidant activity by causing upregulation of various antioxidant enzymes such as SOD, GSH, catalase, and heme-oxygenase 1 (HO-1) via induction of Nuclear factor erythroid 2-related factor 2 (NFE2L2), and downregulation of pro-oxidant enzymes such as inducible nitric oxide synthases and NADPH oxidase. Furthermore, zinc competes with the highly reactive oxidants Cu and Fe for binding with membranous proteins and cell membranes, resulting in their replacement and inhibition of hydroxyl radical formation. It also binds with sulfhydryl groups, resulting in inhibition of lipid peroxidation [5]. The movement of zinc across synapse is responsible for maintenance of synaptic plasticity and long-term potentiation in the hippocampal CA3 neurons of the brain. Maintaining adequate levels of zinc in the synapse requires energy, which gets exhausted with age; this gives a path to zinc supplementation to improve cognitive decline in AD patients [12]. According to the molecular docking study done by Zafar et al., zinc can serve as a potential treatment for AD due to its anticholinesterase and antioxidant activity [13]. Marketed formulations of zinc are Zincovit, Zinconia 50, Zincofer tablet.

Manganese is an essential element used for the activation and synthesis of several enzymes. It exerts antioxidant activity by attenuating the levels of SOD2, thus causing a reduction in oxidative stress.

Selenium is a natural element that forms an essential component of selenoproteins, which are essential components of the antioxidant defense system. Selenium is available in inorganic forms such as selenate, selenite, and selenide, and in organic forms such as selenomethionine and selenocysteine, which are relatively less toxic than the inorganic forms. Selenium is essential for GPX activity, an essential antioxidant enzyme used to reduce oxidative stress-induced damage. Zhang et al. conducted numerous studies that revealed multiple beneficial effects of selenomethionine in AD mice at a dose of 6 μg/ml. Selenomethionine reduced and attenuated Aβ and tau-associated pathology, oxidative stress, synaptic dysfunction, and cognitive decline in AD mice [14]. Marketed formulations of selenium include HS gold softgel capsule and chicnutrix bounce.

1.3.2.2 POLYPHENOLS

Polyphenolic chemicals, which are the main components derived from natural sources, are said to have strong antioxidant potential. The majority of antioxidants that occur naturally besides polyphenols are flavonoids, non-flavonoids, organosulfur compounds, terpenoids, and various vitamins and minerals, which can be found in all sections of plants, including fruits, vegetables, nuts, seeds, leaves, roots, and bark. Recent toxicological investigations on the usage of synthetic antioxidants have revealed some of their undesirable or negative consequences. These reports have compelled scientists to concentrate their efforts on identifying natural sources with adequate antioxidant activity [15].

Polyphenol compounds, which are secondary metabolites, have the most potential antioxidant properties. Polyphenol compounds are further categorized into flavonoids and non-flavonoids based on the number and arrangement of phenol rings in their chemical structure. Non-flavonoids consist of one phenol ring and include stilbenes, curcuminoids, phenolic compounds, and lignans, whereas flavonoids contain two or more phenolic rings connected to three carbon atoms. Flavonoids are most abundantly present and account for 60% of the human diet. Flavonoids are subdivided into various subgroups, which include flavones, flavonols, flavanols, flavanones, isoflavones, flavanonols, and anthocyanins. These phytochemicals exhibit differences in hydroxylation and oxidation states. Polyphenols exhibit antioxidant activity through various mechanistic pathways. One of the mechanisms behind polyphenolic antioxidant activity is free radical scavenging. Polyphenols extend

the conjugation of unpaired electrons of ROS, leading to the formation of a less reactive radical. Consequently, reactive nitrogen species (RNS) and ROS are quenched, allowing polyphenolic compounds to exhibit antioxidant properties [16, 17].

1.3.2.3 NON-FLAVONOIDS

1.3.2.3.1 Stilbenes

Resveratrol is found in berries, nuts, red wine, and various plants. Resveratrol (Figure 1.2) has anti-inflammatory, mitochondrial biogenesis-promoting, mitochondrial respiratory-promoting, and gluconeogenesis-stimulating properties. It is due to these properties that it has been widely used in chronic diseases and is showing potential benefits in AD too. Resveratrol inhibits intracellular and extracellular Aβ plaque deposition, confers antioxidant properties, reduces tau protein phosphorylation, inactivates key target proteins GSK-3β, and activates AMP-dependent protein kinase and silent information regulator 1 (SIRT1). Resveratrol's remarkable antioxidant properties are helpful for providing neuroprotection in Alzheimer's disease. Resveratrol enhances the activity of SOD1, which is a potent antioxidant involved in the catalysis of highly reactive free radicals into less reactive species. Resveratrol also enhances the activity of other antioxidants like catalase and GPx. Resveratrol stimulates silent information regulator 1 (SIRT1) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) expression [18, 19], thus improving the function of the mitochondria. Resveratrol mimics the effect produced by calorie restriction and exercise and confers protection to the mitochondria from oxidative damage in AD [19, 20]. Resveratrol has shown its antioxidant potential in senescence-accelerated mice by attenuating the amounts of GPx and SOD and diminishing malondialdehyde when used at doses of 25, 50, and 100 mg/kg/day for 8 weeks [21, 22]. The pharmacokinetic study of trans-resveratrol consumed in the form of hard capsules at doses of 25, 50, 100, and 150 mg six times a day for thirteen doses showed that it has a high level of tolerance. Its concentration in plasma does not increase with time but rather decreases, and its bioavailability is enhanced by administering it in the morning [23]. Marketed formulations of resveratrol include Biotrex Resveratrol 500 mg, Nutrigrow Resveratrol Veg Capsule, Sharrets Nutritions Resonate Resveratrol, Reffron Tablet, and Decode Age Trans-Resveratrol 250 Vegetable Capsule.

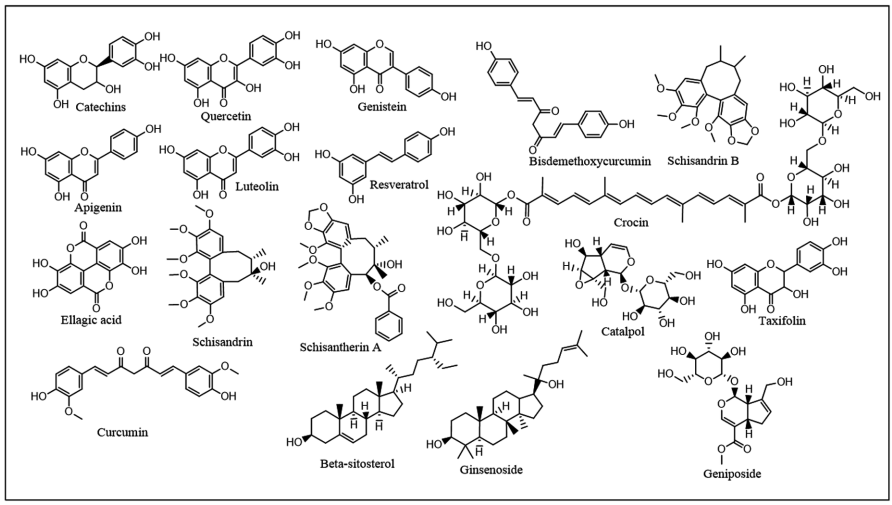

FIGURE 1.2 Natural antioxidants as anti-Alzheimer's agents.

1.3.2.3.2 Phenolic Compounds

Ellagic acid is a dimeric derivative of gallic acid, which is a naturally occurring non-flavonoid of the polyphenolic group. Ellagic acid (Figure 1.2) and flavonoids, particularly a flavonol subclass known as quercetin, are the most abundant phenolic compounds extracted from the leaves of *Eucalyptus globulus.* Ellagic acid is found in high concentration in berries like raspberries, strawberries, blueberries, and grapes and in various distilled beverages [24, 25]. Ellagic acid acts by reducing H_2O_2-induced oxidative stress, boosting the antioxidant enzyme activity, and stimulating GSH levels, causing a decrease in lipid peroxisomal degradation and ROS production. In an animal model of rotenone-induced cell death, ellagic acid has been able to protect cells from apoptosis by reducing the levels of ADP-ribose polymerase-1 (PARP)-induced cleavage. In this model, it has also been able to exert free radical scavenging properties by reducing the levels of peroxynitrite. Ellagic acid has been able to protect PC12 cells from Aβ peptide-induced damage at 0.5–5 µg/ml by inhibiting ROS production and by reducing calcium influx. Furthermore, it has been able to reduce the level of malondialdehyde, which is a lipid peroxidation product [26, 27]. There are two different isoforms of beta secretase (BACE), and it has been recognized that this enzyme's cleaving effect on AβPP is crucial for producing Aβ peptides following gamma secretase action. Ellagic acid has the ability to moderately inhibit BACE-1, which

helps to lessen the harm brought on by the formation of Aβ plaques and the intracellular deposition of neurofibrillary tangles. According to the studies conducted *in vitro*, ellagic acid generated a large decrease of oligomers and was successful in preventing Aβ-induced toxicity. Kwak and colleagues [28] found that it was a moderate BACE-1 specific inhibitor during a search for natural anti-dementia medications [27, 28]. Current commercial ellagic acid preparations include Trexgenics pomegranate extracts 500 mg veg capsules, Herb Essential pomegranate tablet, and Fasczo Jamun capsule.

1.3.2.3.3 Lignans

1. **Schisandrin:** It is the most effective compound of the herb *Schisandra chinensis*. Hu et al. also discovered that schisandrin (Figure 1.2) at doses of 4, 12, and 36 mg/kg body weight could considerably ameliorate the spatial reference memory impairment and short-term memory in mice brought on by the *in vivo* model. Schisandrin may lessen cognitive impairment by antioxidation, causing an increase in the GPx activity and glutathione (GSH) content, and decreasing malondialdehyde and oxidized glutathione (GSSG) levels in the rat brain's hippocampus and cerebral cortex [29].
2. **Schisantherin A:** Major bioactive lignan Schisantherin A (Figure 1.2) was discovered in the fruits of *Schisandra chinensis* and has the ability to treat neurological illnesses brought on by aberrant oxidative stress. Schisantherin A at a dose of 0.1 mg/kg increased GSH-px and SOD production, lowered the amount of Aβ and activity of malondialdehyde in the cerebral cortex and hippocampus in mice. Additionally, it dramatically lessened the hippocampus' histological alterations [30].
3. **Schisandrin B (SchB):** It was shown in an *in vivo* study to greatly boost Ach levels while suppressing AChE activity in scopolamine-induced dementia mouse models. SchB (5, 10, or 20 μM for 10 min) dramatically reduced the generation of ROS and the activity of NADPH oxidase in microglia, thereby protecting neurons. Compounds Schisandrin and Schisantherin increased the expression of SOD and GSH and inhibited MDA in brain tissue, as chemicals Gomisin A and Schisandrin B (Figure 1.2) decreased the amount of ROS to withstand oxidative stress [31,

32]. Marketed formulations of lignans available are lignan extract 30 caps by Source Naturals, Life Extension, Mega GLA, sesame lignans, etc.

4. **Curcuminoids:** A polyphenol called curcumin can be found in the rhizomes of the herb *Curcuma longa Linn,* also known as turmeric. Curcumin (Figure 1.2) has been shown to exhibit anti-inflammatory, neuroprotective, chemoprotective, and antioxidant properties; thus, it has been used in the treatment of chronic illnesses. In AD, curcumin exhibited antioxidant properties by scavenging ROS and RNS. Furthermore, it has been shown to reduce Aβ plaque deposition in AD. An estimation of biomarkers for evaluating its antioxidant potential revealed a reduction of them. However, its use has been limited due to its lower bioavailability caused by lower absorption, rapid metabolism, and rapid excretion. This limitation has been improved by the preparation of various formulations, such as liposomal encapsulations, nanoparticles, emulsions, powder forms, micellar forms, and many more. Furthermore, the individual components of the curcuminoid mixture could be administered separately rather than in combination to maximize benefits. These could also be administered with various foods like vitamin C, K, folate, piperine, and alpha-lipoic acid to increase their benefits in AD patients. In animal studies, the antioxidant effect produced by curcumin is dose-dependently increased. In one such study, curcumin administration at a dosage of 50 mg/kg was shown to exert a beneficial effect on improving cognitive impairment in AD mice. Such improvement was seen as it was able to attenuate the levels of SOD and malondialdehyde in the hippocampal region of SAMP8 mice [33, 34]. The USFDA has given approval to curcuminoids for use, and they are generally regarded as safe medications. It shows a good safety profile even when administered in the dose range of 4,000–8,000 mg and with doses up to 12,000 mg/day [35]. However, it has been reported in human studies to have a ceiling effect, which is why it is best administered in a moderate dose [34, 35]. Marketed formulations of curcumin available are Curkey Curcumin 100 mg Pastilles Soothing Mint, Patanjali Ayurveda Curcumin Gold 95 Immunity Booster Tablet, Snec 30 Liquid Turmeric Curcumin Capsule US Patent, Inlife Curcumin C3 Complex 500 mg Turmeric with BioPerine.

Curcuminoids include curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Bisdemethoxycurcumin (Figure 1.2) has been shown to exert an antioxidant effect in animal models of AD by upregulating SIRT1 when administered at a dose of 5 μg/kg/day via slow injection into the lateral ventricle over 3 minutes in C57BL/6 mice, APP/PS mice, and APP/PS mice treated with EX527, an inhibitor of SIRT1. Silent information regulator 1, or SIRT1, is a member of a family of histone/non-histone deacetylases that relies on nicotinamide adenine dinucleotide (NAD+) for its action. It demonstrates antioxidant properties by controlling various pathways involving SOD, the mammalian forkhead box transcription factor class O (FOXO), nicotinamide adenine dinucleotide phosphate-oxidase (NOX), nuclear factor-κB (NF-κB), and endothelial nitric oxide synthase. Activated SIRT1 has been associated with studies showing its ability to activate downstream targets, reduce oxidative stress, provide neuroprotective effects, and aid in managing AD [36–38].

1.3.2.4 FLAVONOIDS

1.3.2.4.1 Flavanols

Catechins (Figure 1.2) are the naturally occurring flavonoids of the flavanol subclass. Fruits such as grapes, pears, apples, and cherries are rich sources of catechins; besides that, green vegetables, legumes (broad beans and green beans), and tea beverages like green tea also contain catechins. The ester of epigallocatechins and gallic acid, known as epigallocatechin-3-gallate (EGCG), exhibits antioxidant properties and thus is found to be neuroprotective in healthy individuals and in individuals with cognitive impairment in AD. Green tea extracts are rich in epigallocatechin-3-gallate and thus are found to be neuroprotective [39–41]. EGCG binds to tau at its phosphorylation site and produces conformational changes in its 3D structure, thus leading to inhibition of its aggregation. Thus, we can say that EGCG has the potential to improve the selective breakdown of phosphorylated tau species in neurons, which could have significant effects on slowing the progression of AD [42]. In conferring protection against the negative impact of senescence in causing AD-associated pathology, two properties play an important role. One is to prevent premature senescence through antioxidant and DNA-altering activity, and the other is to remove already formed senescent cells.

EGCG has been able to increase the activity of various antioxidant enzymes and, by exhibiting free radical scavenging properties, is able to reduce premature senescence occurring via oxidative damage. EGCG has also been able to reduce the levels of protein carbonyl, which leads to a reduction of age-associated oxidative damage to DNA when used in the dose of 2 mg/kg/day orally for 30 days in male albino rats of Wistar strain [43, 44]. Available marketed catechins preparations include Actilife tablet, Elicura Essential Detox Care, and In life Green Tea Extract 500 mg.

1.3.2.4.2 Flavonols

Quercetin is a flavonoid belonging to the flavonol subclass and has the highest antioxidant potential; it is most abundantly found in higher plants and can be extracted in its free form from surfaces of leaf, bud, or fruit extract. Compositae, Rhamnaceae, Passiflorae are plant families rich in quercetin (Figure 1.2). Apples, berries, onions, asparagus, red leaf lettuce, and capers all have a significant amount of this flavonoid. The anticarcinogenic, anti-inflammatory, anti-infective, and neurostimulant properties of quercetin make it most suitable for human use. The daily recommended dose of quercetin is 1 g/day. While stimulating mitochondrial biogenesis, quercetin also inhibits lipid peroxidation and platelet aggregation. The hydroxyl group in quercetin is responsible for its antioxidant property. Quercetin has been able to exert antioxidant activity by causing a reduction in superoxide free radicals and by its free radical scavenging properties. The molecule has antioxidant potential due to the presence of a catechol group in ring B and a –OH group at the C-3 position. Moreover, it has been able to upregulate levels of NFE2L2 and paraoxonase 2 (PON2) which are important enzymes responsible for imparting the body its own antioxidant potential by further regulating the activity of other enzymes like SOD, catalase, Glutathione-S-transferase, GPx, HO-1, glutamate cysteine ligase, sulfiredoxin, and thioredoxin [45]. Available marketed quercetin compounds include HealthVit quercetin 100 mg, Doctor's Best quercetin bromelain veggie cap, Herbika Quercetin Capsule, Decode Age Quercetin Vegetable capsule.

1.3.2.4.3 Flavanonols

Taxifolin, a flavonoid of subclass flavonols, can be found in a variety of plants, including milk thistle, onions, and the bark of Douglas fir trees.

Taxifolin (Figure 1.2) inhibits the production of Aβ fibrils *in vitro* and has antioxidant effects. Taxifolin's restricted BBB permeability didn't stop it from considerably lowering cerebral lipid peroxidation levels in the brain, a hallmark of oxidative tissue damage. Furthermore, the taxifolin group had lower cerebral expression levels of oxidative stress-response genes. Additionally, taxifolin hindered the brain's ability to produce Aβ. The ability of polyphenols to donate hydrogen as well as their interactions with the proteins involved in intracellular signaling and the activation of cellular signaling pathways all contribute to their antioxidant properties [46].

1.3.2.4.4 Isoflavones

Isoflavones are biomolecules belonging to the class of flavonoids in the polyphenol group. Soybeans and soy products are rich in isoflavones. These sources consist of various types of isoflavones, namely daidzein, glycitein, and genistein. Among them, genistein has the highest concentration. Soybeans, soy extracts, raisins, and currants are rich sources of genistein (Figure 1.2). Apart from that, coffee, alfalfa, cauliflower, broccoli, clover seeds, and sunflower seeds also contain genistein. Genistein mimics estrogenic effects and is thus classified as a phytoestrogen, or plant-derived estrogen. Apart from its use in improving postmenopausal symptoms, it has also been used to improve cognitive impairment in AD patients. Genistein has been able to ameliorate Aβ peptide-induced oxidative damage by causing upregulation of the Nrf2 signaling pathway and by its free radical scavenging property. By the aforementioned method, genistein at a concentration of 0.1 and 40 μM attenuated Aβ-stimulated decrease in neuronal cell survival rate by 7.2% and 13.9%, respectively [47, 48]. Available marketed formulations of genistein include Palmiges Capsule, West-Coast Manoneed Original tablet, Unived Menopause Management Vegan Capsule.

1.3.2.4.5 Flavones and Flavanones

Apigenin is a flavonoid of the flavone subclass and is found in the highest concentration in chamomile flowers. Other sources of apigenin (Figure 1.2) include celery, parsley, and grapefruit. In animal models, particularly in the Aβ-induced amnesia mouse model, apigenin has been shown to improve memory and spatial learning when a dose of 20 mg/kg is administered. The latter effect has been shown to be due to antioxidant activity. Apigenin's antioxidant potential is attributed to its free radical scavenging activity as

well as its ability to increase the activity of SOD and GPx [49]. Current commercial apigenin-containing preparations include Trexgenics chamomile flower extract 1.2% apigenin 600 mg capsule, medpro A hair serum, pharmtech celery capsule, etc.

Several vegetables, including celery, parsley, thyme, peppermint, and oregano, contain the flavone component luteolin. The antioxidant activity of luteolin (Figure 1.2) in a streptozotocin-induced diabetic model has been related to enhancements in cognitive function as a result of treatment. Chronic luteolin administration (50, 100 mg/kg over 8 weeks) can lessen neuronal damage and enhance cognitive function. The capacity of luteolin to increase antioxidant activity is connected to this action. In diabetes, lipid peroxidation rises while antioxidant enzyme activity is reduced in the hippocampus and cortex. Chronic luteolin therapy, however, can lessen the type 2 diabetes mellitus-related changes. Thus, we can say that luteolin antioxidant activity potential might further help to prevent AD progression [50]. Marketed formulations of luteolin include Pomeroz capsule, biomedison 2WiN Veg capsule.

Anthocyanins-NFE2L2 is a key regulatory gene in mediating oxidative stress as its expression leads to activation of various antioxidant enzymes like HO and glutathione cysteine ligase modulatory subunit (GCLM) through phosphorylated PI3Ks or phosphatidylinositol 3-kinase, phosphorylated Akt, and phosphorylated glycogen synthase kinase 3 beta pathways (GSK3b). In AD, activation of the latter pathway is decreased; therefore, activation of such pathways can increase signaling processes and pathways involving various antioxidant enzymes. Anthocyanin, present in high concentration in Korean black beans, has been shown to reduce synaptic dysfunction and neurodegeneration by causing upregulation of the GSK3b/Nrf2/PI3K pathways in an *in vitro* model when administered at a dose of 12 mg/kg/day intraperitoneally for thirty days in an APP/PS1 transgenic mouse model of AD [51]. Marketed formulations of anthocyanins include PHYTORELIEF-CC lozenges.

1.3.2.5 TERPENOIDS

1.3.2.5.1 Carotenoids

Carotenoids are consumed via fruits, vegetables, and seafood. These chromophoric compounds impart yellow, red, and orange color to the various foods in which they are present, and they are mostly water-insoluble. There are

various types of carotenoids, including alpha-carotene, beta-cryptoxanthin, beta-carotene, lycopene, lutein, zeaxanthin, and astaxanthin. Although all carotenoids have antioxidant activity, alpha-carotene, beta-carotene, and beta-cryptoxanthin have provitamin A activity as they are converted into retinol inside the body and exhibit vitamin A activity. Chemically, carotenoids are divided into two types: xanthophylls (beta-cryptoxanthin, lutein, zeaxanthin, and astaxanthin) and carotenes (alpha-carotene, lycopene, and beta-carotene). They exhibit antioxidant potential by scavenging ROS and RNS, which are elevated in AD individuals, and thus they can be utilized in attenuating cognitive decline in AD patients. It has been discovered that the levels of various carotenoids (alpha-carotene, beta-carotene, lutein, and lycopene) are inversely related to the amount of lymphocyte DNA content containing the oxidized base, 8-OHdG; additionally, it has been discovered that lycopene, found in tomatoes, cranberries, watermelon, grapes, papayas, and apricots, tends to reduce oxidative damage caused to the DNA, Either by causing a reduction in strand breakdown or by increasing DNA resistance to ROS-induced damage. Lycopene and xanthophylls have also been shown to scavenge biomarkers of lipid and DNA oxidation in humans and thus can serve as a potential treatment option for treating or halting the progression of the disease [52]. Lycopene, when a dose of 5 mg/kg was given for 35 days in combination with human amniotic epithelial cells, attenuated cognitive decline in AD rats [53].

Marketed formulations of carotenoids include A to Z NS+ tablet, Fertisure M nutraceutical tablet, Absolut Women capsule, and SM Fibro soft gelatin capsule.

Crocin, obtained from *Crocus sativus* L. extract (saffron), is a yellow-colored carotenoid which has shown to exhibit anti-inflammatory, antioxidant, antidepressant, and memory improvement activity. Crocin (Figure 1.2) is somewhat different from other carotenoid compounds as it is water-soluble due to the presence of a sugar moiety attached to the carboxylic acid group found in crocetin. Crocin is mainly responsible for the beneficial effects shown by the use of saffron. Various clinical studies have revealed crocin to be nearly as effective as donepezil and memantine in providing cognition-improving effects in patients with mild-to-moderate and moderate-to-severe AD. According to *in vitro* and animal research studies, crocin may have neuroprotective effects as well as benefits for memory and cognition [54, 55]. In Wistar rats, it has been shown to improve cognitive function through its antioxidant activity when administered at a dose of 5 or 20 mg/kg, i.g., crocin every day. Crocin has been shown to improve the viability of HT22

cells after l-glutamate-induced damage by causing antiapoptotic effects, mitigating mitochondrial dysfunction, suppressing intracellular ROS accumulation, and by preventing calcium overload when compared to untreated cells [54]. Marketed formulations of crocin include Lion Brand Saffron and Vedkarma.

1.3.2.5.2 Terpenes

1. **Ginsenosides:** These are a class of triterpene saponins. Ginsenoside, which is obtained from the roots of the plant *Panax ginseng*, has been widely used in China and other Asian countries to improve intelligence. Furthermore, it has been used to treat amnesia, which is the hallmark clinical symptom of AD. Ginsenosides (Figure 1.2) are divided into two categories based on their chemical structure: protopanaxadiol (PPD) and protopanaxatriol (PPT). Ginsenoside Rg1 is a type of PPT, is present in the highest concentration, and is the most efficacious component of the ginseng root extract. Ginsenoside has been found to ameliorate cognitive impairment in AD patients by modulating synapses and through its antioxidant and anti-inflammatory activity. Formulations to treat amnesia containing ginseng extract include Kaixin Powder, Yangxin Decoction, and Tianwang Buxin Pills.

   The antioxidant activity of ginsenosides has been utilized in AD to improve cognitive impairment and reduce apoptosis-induced neurodegeneration. Ginsenosides not only improve the activity of antioxidant enzymes but also reduce ROS production from its source. Ginsenosides reduce the levels of malondialdehyde and 8-hydroxydeoxyguanosine production in the brain tissues of a mouse model. This is shown by their ability to restore the activity of SOD and GPx. Furthermore, they have been shown to inhibit ROS production in the shrew model of AD by decreasing the expression of p47phox, p22phox, RAC1, and NADPH oxidase-2 (NOX2), thus improving cognitive function at a dose of 30 mg/kg/day [56, 57]. Marketed formulations of ginsenosides include Nature's Bounty Ginseng Complex Capsule, Zenith Nutrition Ginseng, Ginst 15, and Nirvasa Korean Ginseng Capsule.

2. **Phytosterols:** These are compounds obtained from various oils (sunflower, olive, and seed oils), peanuts, cereals, almonds, avacado,

and vegetables. These can also be obtained from parts of various medicinal plants, like *Hydnophytum formicarum, Spilanthes acmella Murr, Coriandrum sativum,* and *Sargassum fusiforme*. Because phytosterols have cholesterol-lowering properties, they are commonly used in the treatment of dyslipidemia. Phytosterols also possess anti-cancer, anti-atherosclerotic, and antioxidant activities. One of the phytosterols, stigmasterol, has been recently employed for use in the treatment of neurodegenerative diseases as it can pass the BBB and has antioxidant potential. Stigmasterol can be obtained from various sources, such as various fruits, vegetables, and berries, including carrots, parsley, kiwi, alfalfa, and peanuts. The structure of stigmasterol closely resembles that of cholesterol except for the carbon double bond at the C-22 position. Stigmasterol has been found to be an effective treatment for AD because it inhibits acetylcholinesterase and reduces the activity of the beta-secretase enzyme on amyloid beta-protein precursor (Aβpp) *in vitro*. Additionally, when H_2O_2-induced cell death was examined *in vitro* using human neuronal cells, it was found that pretreatment with 1 μM of stigmasterol reduced the level of ROS and attenuated the oxidative stress-induced cell death. It was observed that it also increased the levels of SIRT1 and forkhead Box-O (FoxO) 3a, caspase, and the antiapoptotic protein B-cell lymphoma (Bcl-2) inside the neurons [58].

1.3.2.5.3 Saponin

1. **Platycodon grandiflorum (PG):** It is an herbaceous plant belonging to the family Campanulaceae. *Platycodon grandiflorum* contains 20 saponins, including platycodin D, platycoside E, and polygalacin D. It exhibits antibacterial, anti-inflammatory, analgesic, and antioxidant effects similar to ginseng saponins, having the structure of an oleanane triterpene as an aglycone. *P. grandiflorum* crude saponin (PGS) confers neuroprotective effects through its ability to ameliorate Aβ-induced oxidative damage in hippocampal cells (HT22), as illustrated in both *in vivo* and *in vitro* model of mice when treated with 5, 10, and 20 μg/ml of PGS. The underlying mechanism behind such an effect was evaluated by estimating the levels of protein through western blotting and by estimating ROS levels through fluorescence microscopy, and it was observed that ROS levels were decreased in

the PGS-treated group compared to the control group. Furthermore, this effect was demonstrated by upregulation of NFE2L2 levels, which is an important transcription factor involved in the activation of various signaling pathways involving antioxidant enzymes such as SOD, HO-1, CAT, and GPx [59].

2. **β-Sitosterol:** It is one of the main phytosterols and belongs to a class of organic compounds known as stigmastanes. These are sterol lipids with structures based on the stigma skeleton. Avocados, peanut oil, corn oil, wheat germ, rice bran, soybeans, and various fruits are rich sources of *β*-sitosterol. *β*-sitosterol (Figure 1.2) has acetylcholine-esterase inhibitory activity both *in vitro* and *in vivo* models. It protects the brain from oxidative damage by increasing the activity of antioxidant enzymes via the PI3-kinase pathway or estrogen receptor activation. Furthermore, it enhances GPx activity, indicating free radical scavenging ability in addition to inhibiting glucose oxidase-mediated oxidative stress and lipid peroxidation by incorporating itself into the membrane, thus reflecting its neuroprotective role in AD. *β*-sitosterol restored working memory, behavioral deficits, and motor coordination in a transgenic animal model of mice. In this *in vitro* model study, the anti-radical and the AD-modifying activity of *β*-sitosterol was evident at a concentration of 120 μg/ml [60–62]. Marketed formulations include NOW Foods Beta-Sitosterol Plant Sterols Softgel and Dr. Palep's Safed Musli Capsule.

1.3.2.5.4 Iridoids

1. **Catalpol:** It is an iridoid glucoside that is isolated from the genus *Rehmannia* (Orobanchaceae). Catalpol (Figure 1.2) confers neuroprotection in AD by reducing oxidative stress, inducing antioxidant enzymes such as GPx, SOD, and catalase, as well as decreasing A*β* senile plaque deposition and increasing its clearance by upregulating insulin-degrading enzyme (IDE) expression in brain tissues. Catalpol has been shown to be effective in a mouse model of AD (10 months old) when given a dosage of 20 mg/kg for 30 days, as it causes a reduction in senile plaque accumulation and has been shown to improve cognitive impairment. Catalpol treatment in cortical astrocyte cell culture has conferred protection to astrocytes against

H_2O_2-induced damage by maintaining glutathione homeostasis and causing upregulation of GPx and catalase [63, 64].

2. **Geniposide:** An iridoid glucoside called Geniposide was isolated from the fruits of *Gardenia jasminoides.* Geniposide (Figure 1.2) protects cortical neuron cultures from Aβ-induced toxicity by reducing oxidative stress-induced damage by upregulating IDE, which increases Aβ plaque clearance by causing the degradation of Aβ senile plaques and thus reduces the Aβ-induced increase in ROS levels. Moreover, in P-12 cells, it has been shown to confer neuroprotection against H_2O_2-induced damage by upregulating the level of the antioxidant enzyme HO-1 and the antiapoptotic protein Bcl-2. Intragastric administration of geniposide in the APP/PC1 mouse model demonstrated neuroprotection by lowering oxidative stress in the mitochondria and raising the potential of the mitochondrial membrane and Cytochrome-C oxidase activity. Furthermore, when geniposide was given at a dosage of 25 mg/kg, i.g., for three months, it resulted in the suppression of Aβ accumulation as well as the improvement of deficits in memory and learning in the AD mouse model [64–66].

1.4 CONCLUSION AND FUTURE PERSPECTIVE

Even though research has been done to investigate the pathogenesis and etiology of AD, much of it remains unknown, which is why the disease remains untreatable as there is no current treatment available that can reverse or counteract the occurrence of the disease. However, naturally available antioxidants have been shown to combat oxidative stress and thus serve as a potential therapy for AD. These substances act by several mechanisms, including upregulation of protective genes and proteins; downregulation of damaging proteins and genes; and by exhibiting free radical scavenging activity. Nevertheless, the use of natural antioxidants as an antioxidant therapy in AD is limited. Vitamins, minerals, carotenoids, and polyphenols available have shown promising effects in combating oxidative stress in animal and cellular models of AD, prompting their research in human clinical trials, both alone and in combination with other approved drugs used in AD. Clinical studies illustrate only a minimal effect of the latter therapy in humans due to their variability in pharmacokinetic parameters. Additional research is needed to improve their pharmacokinetic properties.

KEYWORDS

- **Alzheimer's disease**
- **cellular models**
- **natural sources**
- **oxidative stress**
- **pathology**
- **pharmacokinetic properties**
- **polyphenols**
- **protective genes**
- **toxicity**

Notes

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CHAPTER 2

Exploring Beta Secretase Inhibitors as the Evergreen Drug Target for Alzheimer's Disease: Calling Herbal Therapies to the Rescue

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ABSTRACT

Alzheimer's disease, one of the most widespread neurodegenerative conditions, entails the deterioration of cognitive and memory capacity, impaired learning, dementia, and behavioral problems. The condition causes disruption in interneuronal signaling and brain atrophy. The amyloid beta cascade

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is the most pertinent and widely accepted version out of all the multiple AD pathogenesis. It proposes that Aβ monomers are produced as a result of APP cleavage preceded by the conversion of these monomers into toxic oligomers, which in turn give rise to sheets, fibrils, and plaques. The β-secretase enzyme catalyzes the rate-determining step of the process of formation of Aβ plaques. Many synthetic drugs have been formulated for targeting this enzyme to halt the disease progression. However, the accompanying side effects have led to their withdrawal. Hence, the researchers have shifted their focus to herbal drugs and phytoconstituents that cause the inhibition of β-secretase. A number of phytoconstituents like alkaloids, flavonoids, glycosides, etc., isolated from various plants have demonstrated significant BACE1 inhibition *in vitro*. The chapter elaborates on the Aβ pathophysiology and the role of the β-secretase enzyme along with herbal therapies that can be used to disrupt the formation of toxic Aβ oligomers and thus stop the disease progression.

2.1 INTRODUCTION

Alzheimer's Association's Facts and Figures Report (2023) is enough to indicate the severity and havoc of this deadly disorder. According to the findings, about 1 in 9 Americans aged 65 and older are suffering from Alzheimer's dementia. By 2023, an estimated 6.7 million Americans aged 65 and older are living with this disorder, and with its accelerating occurrence, by 2050, the number of people suffering from Alzheimer's disease (AD) is projected to be around 88 million [1]. The global statistics indicate 315 million people suffering from preclinical AD, 69 million with prodromal AD, and 32 million people with AD dementia, which makes up to 416 million people in total suffering from this debilitating disorder or 22% of all persons aged 50 and above [2]. The disorder being progressive neurodegenerative in nature ultimately leads to neuropathic conditions debilitating the mental, cognitive, functional, and behavioral abilities of the patients. The disease is a combination of several pathological abnormalities starting from the deposition of neuritic plaques and neurofibrillary tangles to the abnormalities in the brain apoptosis, elevated inflammation, oxidative stress, mitochondrial dysfunction, and synaptic dysfunction. All of which ultimately lead to the death of an individual [3]. Alterations in the concentration of acetylcholine neurotransmitter also work as a prime event in the progression of this deadly disease. Although, besides in-depth knowledge of the complete mechanism and ample research being conducted all across the world, the ultimate solution for this problem hasn't yet been discovered. The currently approved treatment regimen for AD focuses on either the cholinergic pathway, like

the acetylcholine inhibitors (rivastigmine, donepezil, galantamine, tacrine) and NMDA receptor agonists like memantine [4]. Although the available therapies do provide symptomatic relief, they do not completely alleviate the underlying pathology. Hence, scientists are trying to explore and target other pathways like the Amyloid cascade, tau pathology, etc. The current chapter focuses on the *β*-amyloid cascade hypothesis and the pioneering role of the *β*-secretase enzyme in the cleavage of APP and formation of A*β* plaques, which ultimately aggravate the condition. It will also explore the potential of various herbal phytoconstituents as *β*-site amyloid precursor protein (APP) cleaving enzyme (BACE1) inhibitors, which can serve as a ray of hope in this journey of drug discovery for AD management.

2.2 APP AND BETA SECRETASE: ITS IMPORTANCE AS THE TARGET

Alzheimer's disease is categorized into 2 classes, namely Familial AD and sporadic AD. FAD, which constitutes only about 5–10% of the AD cases, is found to be connected to mutations in the *APP* gene and *Presenilin-1* and *Presenilin-2* genes, which reside on chromosomes 21, 14, and 1, respectively. Apolipoprotein E4 has also been found to trigger a slight predisposition to AD [5]. Amyloid-*β* plaques, composed of A*β* peptides which are themselves made up of 38–43 amino acids, form the primary histopathological hallmark of AD. A*β* is mainly generated by neurons in the brain. It is formed as a result of sequential proteolysis of the type-1 membrane protein APP. It is first cleaved by the *β*-secretase enzyme, converting it into sAPP*β* and the C99 segment. This segment is further cleaved by the γ-secretase enzyme, composed of 4 transmembrane proteins (presenilin, nicastrin, Pen2, and Aph1), which results in the liberation of A*β*. A*β* is not cleared up by the cellular mechanism and starts accumulating in the subcellular components. It is released freely in the interstitial fluid of the brain, hampering its normal physiological functions and triggering severe pathological changes leading to dementia [4]. A third protease, α-secretase, acts on APP resulting in the formation of sAPPα and the C-terminal fragment C83, which on further cleavage by the γ-secretase enzyme leads to the formation of P3 and ACID domains that are easily cleared from the neurons by cellular machinery [6].

2.2.1 BACE-1 ENZYME

Beta-site amyloid precursor protein cleaving enzyme is an aspartyl protease belonging to the pepsin family discovered in 1999. It is a type-1

transmembrane protein highly expressed in the brain, specifically localized in neurons, oligodendrocytes, and astrocytes [7]. Its concentration is generally identified to be elevated in neurons surrounding amyloid plaques [8]. The BACE1 enzyme is directly involved in amyloidogenesis and catalyzes the rate-determining step of the proteolytic reactions resulting in the accumulation of plaques by cleaving the extracellular domain of APP. The catalytic aspartic residues responsible for the catalytic activity of the BACE1 enzyme in cleaving the APP to form the N-terminus of the Aβ peptide and the C99 fragment are located at Asp 32 and Asp 228. Several synthetic drugs have been designed to target the BACE1 enzyme, some of which have also reached clinical trials and yielded successful results [9]. But as of now, no molecule is clinically available for the management of AD. Small molecular inhibitors like Lanabecestat were terminated in their Phase 3 trials due to less efficacy [Clinicaltrials.gov ID: NCT02245737]; Atabecestat was also terminated in a Phase 2/3 trial due to observed liver toxicity [Clinicaltrials.gov ID: NCT02569398]; Elenbecestat is currently in Phase 3 trials but side effects like dermatitis, headache, falls, nightmares have been evident [Clinicaltrials.gov ID: NCT03036280]; Verubecestat has also been withdrawn from Phase 3 trials due to behavioral side effects [Clinicaltrials.gov ID: NCT01953601] and LY320262 was also withdrawn from Phase 2 due to less clinical efficacy [Clinicaltrials.gov ID: NCT02323334]. Similarly, many more of such synthetic drugs have been tried and tested which did cause improvement in patient conditions, but have yielded major side effects. Hence, the researchers have now started exploring Herbal therapies for the management of this deadly disorder and also minimizing the adverse side effects occurring due to these.

2.3 PUTTING HERBAL THERAPIES TO THE RESCUE

Ever since the advent of mankind, natural products have been used as medicine for all kinds of ailments. These harbor a rich source of medicinally active phytoconstituents that are effective in curing severe diseases. A multitude of plant extracts and constituents have been identified as effective in the management of memory disorders [10, 11]. These may also prove to be a savior in managing AD. Besides being effective, these have reduced side effects and enhanced biocompatibility in practical applications. The chapter explores the neuroprotective action of some of the natural compounds along with their efficacy in reducing the concentration of Aβ. The phytoconstituents

extracted from the extracts of daily-use household plants like Curcuma longa, Centella asiatica, Olea europaea have demonstrated significant efficacy in inhibiting the formation and aggregation of Aβ plaques by halting the BACE1 enzyme action and also facilitated in promoting its clearance. Thus, these enhance the memory and cognitive abilities of the mice [4, 12].

2.4 PHYTOCONSTITUENT CLASSES EXHIBITING BACE1 INHIBITORY EFFECT

2.4.1 ALKALOIDS

The two protoberberine alkaloids named groenlandicine and epiberberine, isolated from *Coptidis rhizoma,* were found to exhibit significant dose-dependent BACE1 inhibition with IC_{50} values of 19.68 μM and 8.55 μM [13, 14]. Alkaloids like northalifoline, neferine, and liensinine isolated from various parts of the plant Nelumbo nucifera (Family: Nelumbonaceae) also demonstrated significant BACE1 inhibition when evaluated using *in-vitro* BACE1 enzyme assay. Liensinine showed the most significant BACE1 inhibition with an IC_{50} value of 6.37 μM. Other alkaloids isolated from the plant also caused inhibition, with neferine having an IC_{50} value of 28.51 μM, while northalifoline had an IC_{50} value of 33.23 μM [15] (Figure 2.1).

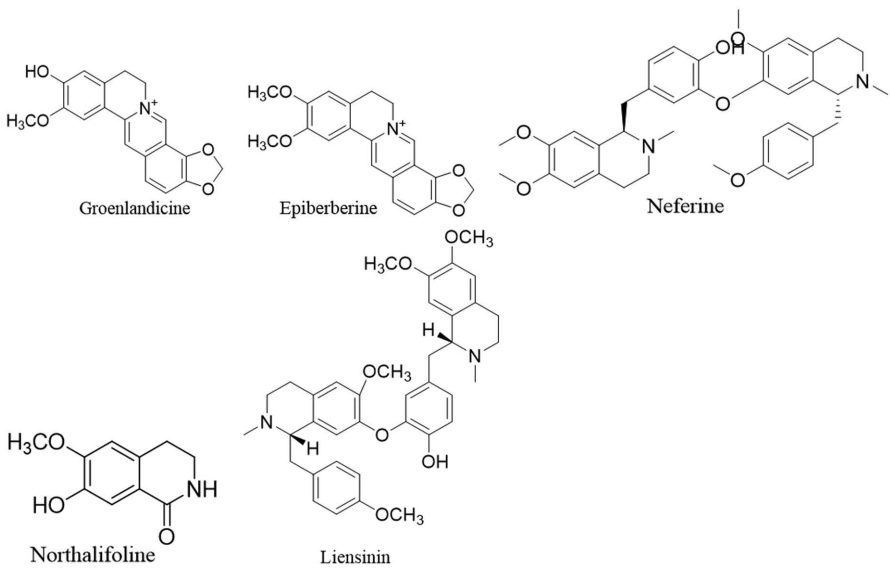


FIGURE 2.1 Structures of alkaloids possessing BACE1 inhibitory activity.

2.4.2 PHENOLIC ACIDS

Phenolic acids like 2-[(Z)-heptadec-11-en-1]-6-hydroxybenzoic acid, 2-[(6Z,9Z,12Z)-heptadeca-6,9,12-trien-1]-6-hydroxybenzoic acid, 2-[(9Z,12Z)-heptadeca-9,12-dienyl]-6-hydroxybenzoic acid, and 2-hydroxy-6-(12-phenyl dodecyl)benzoic acid extracted from ethanol extract of rhizomes of Homalomena occulta (Family: Araceae) exhibited non-competitive BACE1 inhibition with respective IC_{50} values being 6.23±0.94 μM, 6.28±0.63 μM, 7.93±0.38 μM, and 7.65±0.62 μM [16] (Figure 2.2).

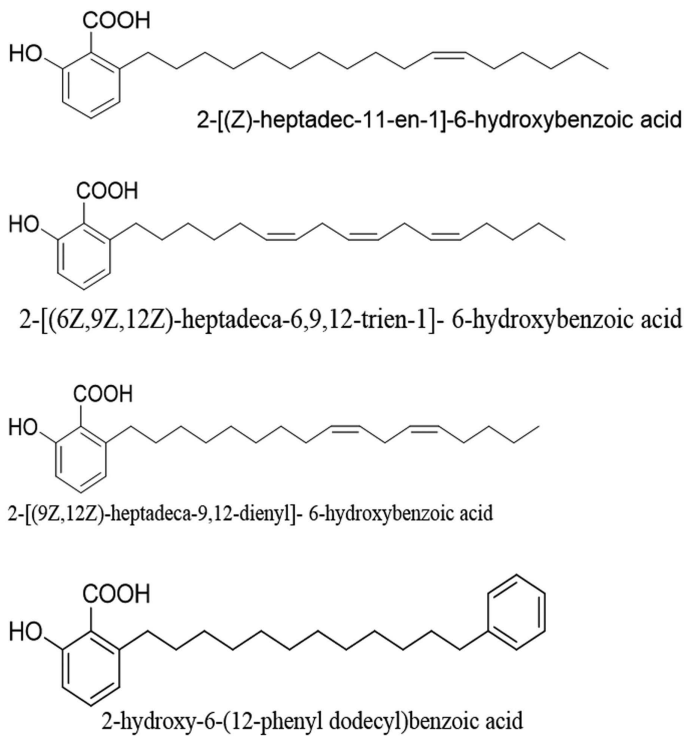


FIGURE 2.2 Structures of phenolic acids possessing BACE1 inhibitory activity.

2.4.3 GLYCOSIDES

Pterosin glycoside, namely (-)-pteroside N and sesquiterpene pterosinone isolated from *Pteridium aquilinum* showed BACE1 inhibition with IC_{50} values of 30.6 μM and 19.4 μM, respectively [17]. Glycosides derived from

Cassia obtusifolia Linn. also showed potential for BACE1 inhibition. The IC_{50} values for the 6 derived glycosides are rubrofusarin [IC_{50} value = 90.01 μM]; rubrofurasin 6-O-*β*-D-glucopyranoside [IC_{50} value = 190.63 μM]; norrubrofurasin 6-O-*β*-D-glucopyranoside [IC_{50} value = 14.41 μM]; isorubrofurasin 10-O-*β*-D-gentiopyranoside [IC_{50} value > 200 μM]; and rubrofurasin 6-O-*β*-D-triglucoside [IC_{50} value > 200 μM] [18] (Figure 2.3).

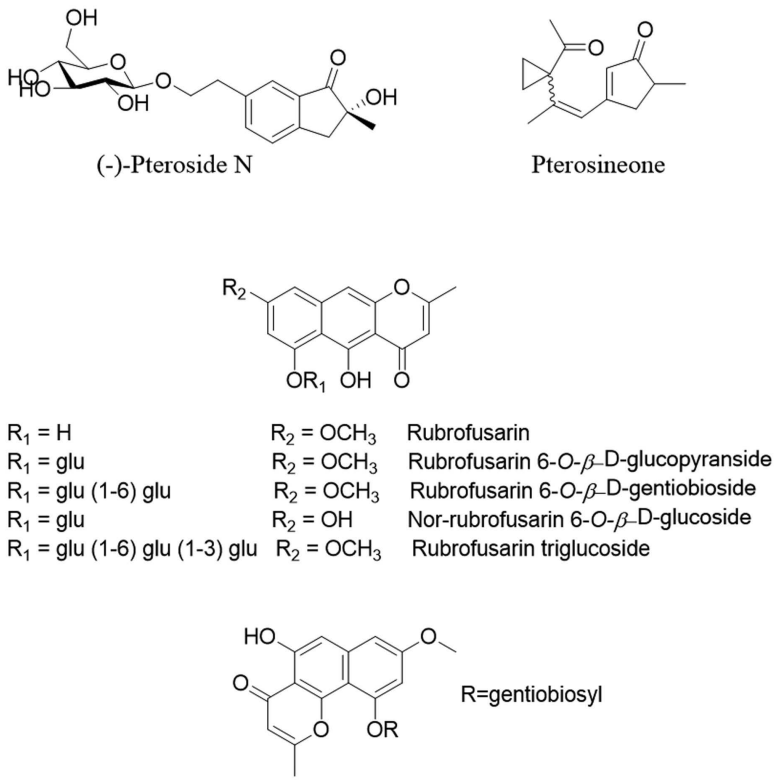

(-)-Pteroside N
Pterosineone
R1 = H R2 = OCH3 Rubrofusarin
R1 = glu R2 = OCH3 Rubrofusarin 6-O-β-D-glucopyranside
R1 = glu (1-6) glu R2 = OCH3 Rubrofusarin 6-O-β-D-gentiobioside
R1 = glu R2 = OH Nor-rubrofusarin 6-O-β-D-glucoside
R1 = glu (1-6) glu (1-3) glu R2 = OCH3 Rubrofusarin triglucoside
R=gentiobiosyl

FIGURE 2.3 Structures of glycosides possessing BACE1 inhibitory activity.

2.4.4 COUMARINS

Fluorocoumarins like isoimperatorin, imperatorin, oxypeucedanin, byakangelicin, and byakangelicol were extracted from the chloroform extract of the roots of *Angelica dahurica* (Family: Umbelliferae) and were evaluated for BACE1 inhibition activity. Researchers found that these exerted dose-dependent inhibition of the BACE1 enzyme at a concentration of 500 μM.

Imperatorin was found to be the most potent with an IC_{50} value of 91.8±7.5 μM [19] (Figure 2.4).

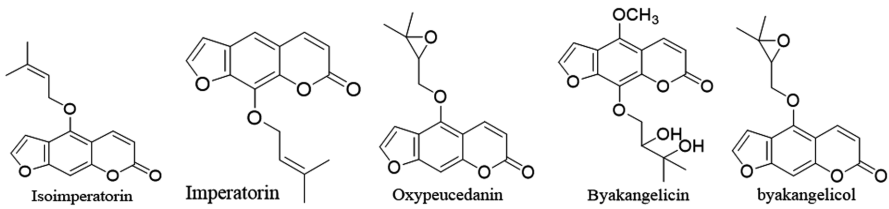


FIGURE 2.4 Structures of coumarins possessing BACE1 inhibitory activity.

2.4.5 TANNINS

Tannins like ellagic acid and punicalagin isolated from ethyl acetate and n-butanol fractions partitioned out from the ethanol extract of the husk of the plant *Punica granatum* (Family: Punicaceae) illustrated dose-dependent inhibition of BACE1 enzyme at concentrations ranging from 0.01–40 μM [20]. Phlorotannins like eckol, dieckol, and 8,8′-bieckol isolated from *Ecklonia cava* (Family: Lessoniaceae) also showed significant BACE1 inhibition with IC_{50} value = 1.62±0.14 μM. Dose-dependent inhibition of the enzyme was exhibited by phlorotannins isolated from the ethyl acetate fraction of the plant *Eisenia bicyclis* (Family: Lessoniaceae) when evaluated using BACE1 FRET assay. The IC_{50} values of the derived phlorotannins were dioxinodehydroeckol (IC_{50} value = 5.35 μM), eckol (IC_{50} value = 12.20 μM), phlorofurofucoeckol-A (IC_{50} value = 2.13 μM), dieckol (IC_{50} value = 2.21 μM), triphloroethol-A (IC_{50} value = 11.68 μM), and 7-phloroethol ($IC_{5}0$ value = 8.59 μM) (Figure 2.5).

2.4.6 FLAVONOIDS

Isoflavonoid, C-methylrotenone (Boeravinone E) extracted from the suspension culture of plant *Abronia Nana* (Family: Nyctaginaceae) was found to exhibit dose-dependent noncompetitive inhibition with IC_{50} value of 5.57 μM [23]. Other flavonoids like Boeravinone D and Mirabijalone D derived from the plant also showed non-competitive BACE1 inhibition [24]. Another flavonoid, galangin, derived from Alpinia Officinarum inhibited BACE1 expression in the human neuroblastoma cell line, SH-SY5Y cells. Galangin at a concentration of 30 μM caused about 60.81±0.58% decrease

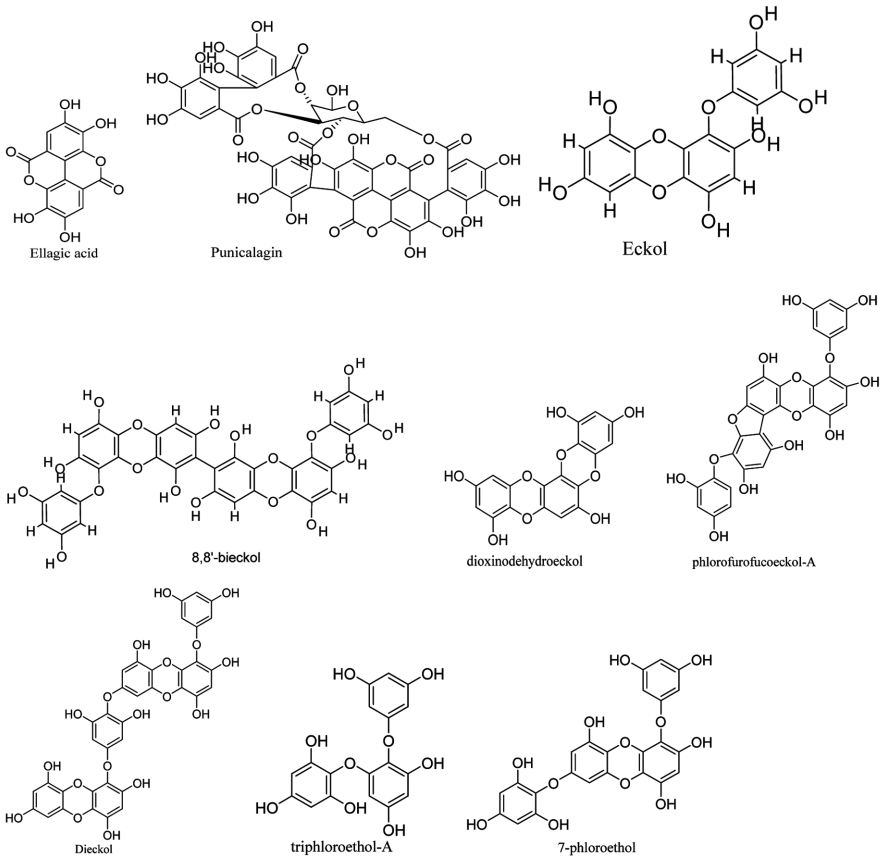


FIGURE 2.5 Structures of tannins possessing BACE1 inhibitory activity.

in the mRNA levels of the enzyme 25]. Flavonones and dihydrochalcones isolated from the ethanol extract of *Balanophora involucrate* (Family: Balanophoraceae) showed <50% BACE1 inhibition at 10 μM dose. Amentoflavone-7,7′-dimethylether isolated from *Cephalotaxus Harrington* var. harringtonia (Family: Cephalotaxaceae) inhibited BACE1 enzyme with an IC_{50} value of 6.25 μM 11, 27]. Bilobetin, ginkgetin, 2,3-dihydro-6-methylginkgetin were major amentoflavone-type bioflavonoids isolated from *Cephalotaxus harringtonia* var. Fastigiata (Family: Cephalotaxaceae). These exerted significant BACE1 inhibitory action when analyzed using BACE1 FRET assay with IC_{50} value of 2.02 μM, 4.18 μM, and 0.35 μM, respectively. Bioflavonoids like amentoflavone and sesquoiaflavone isolated from *Cunninghamia Lanceolata* (Family: Cupressaceae) exhibited notable

BACE1 inhibition with IC_{50} value of 1.54 μM for amentoflavone and 1.40 μM for sesquiflavone [27] (Figure 2.6). Some of the other significant flavonoids illustrating significant BACE1 inhibition are listed in Table 2.1.

TABLE 2.1 Some of the Flavonoids Demonstrating Notable BACE1 Inhibition

Flavonoids	Plant Name and Family	Result	References
Sebestenoids A, B, C, D	*Cordia sebestena* (Family: Boraginaceae)	Sebestenoid exerted potent inhibitory action with IC_{50} value being 20 and 22 μM, respectively. Other 2 sebestenoids also exerted BACE1 inhibition with IC_{50} values of 32 and 116 μM.	[28]
2,3-dihydroamentofalvone	Cycas revolute (Family: Cycadaceae)	Potent BACE1 inhibition effects (IC_{50} value= 0.75 μM).	[27]
Podocarpus flavone A, Podocarpus flavone B, isoginkgetin.	*Podocarpus macrophyllus* var. *Macrophyllus* (Family: Podocarpaceae).	IC_{50} value of the 3 biflavonoids were found out to be 0.99 μM, 4.21 μM and 3.01 μM, respectively.	[27]
Luteolin	*Perilla frutescens* (Family: Lamiaceae)	IC_{50} value= 5.0×10−7 μM.	[29]
Norartocarpetin, kuwanon C, morusin, cyclomorusin, kuwanon A, morusinol, neocyclomorusin, mormin.	*Morus ihou* (Family: Moraceae)	Kuwanon C (IC_{50} value = 3.4±1.3 Mm), morusin (IC_{50} value = 59.4±12.7 Mm), cyclomorusin (IC_{50} value = 101.2±5.3 Mm), kuwanon A (IC_{50} value = 5.3±0.2 Mm), morusinol (IC_{50} value = 135.9±22.8 Mm), neocyclomorusin (IC_{50} value = 103.5±17.4 Mm), mormin (IC_{50} value = 103.5±17.4 Mm).	[30]
Isoflavones [5,7,2′,4′-tetrahydroxy-8-(3,7-dimethyl-2,6-octadienyl)]; Lupiwhiteone: Coumarano-chroman-4-one [3,5,7-trihydroxy-4′-methoxycoumarano-chroman-4-one]; 6-(3-methyl-2-buten-1-yl)-3,5,7-trihydroxy-4′-methoxycoumarano-chroman-4-one.	*Ficus benjamina* var, nuda.	5,7,2′,4′-tetrahydroxy-8-(3,7-dimethyl-2,6-octadienyl) [IC_{50} value= 45±3 μM]; Lupiwhiteone [IC_{50} value= 27±4 μM]; [3,5,7-trihydroxy-4′-methoxycoumarano-chroman-4-one] [IC_{50} value= 139±10 μM]; 6-(3-methyl-2-buten-1-yl)-3,5,7-trihydroxy-4′-methoxycoumarano-chroman-4-one [IC_{50} value= 91±13 μM].	[31]

TABLE 2.1 *(Continued)*

Flavonoids	Plant Name and Family	Result	References
2,2′,4′-Trihydroxychalcone	*Glycyrrhiza glabra* (Family: Fabaceae).	Competitive BACE1 enzyme inhibition IC_{50} value= 2.45 μM. It was found to ameliorate memory impairment in mice model HEK293-APP. Concentration-dependent decrease in the levels of $A\beta_{40}$ and $A\beta_{42}$.	[32]
Isovitexin, vitexin, apigenin, quercetrin	Bamboo leaves *Serjania erecta* (Family: Sapindaceae).	BACE1 inhibition of each flavonoid is Vitexin [IC_{50} value= 51.07 μM], Isovitexin [IC_{50} value= >100 μM], Apigenin [IC_{50} value >100 μM], quercetin [IC_{50} value= 7.41 μM].	[33]

2.4.7 TERPENOIDS

The n-hexane fraction of roots of the plant *Aralia cordata* (Family: Araliaceae) gave rise to multiple ent-pimarene-type diterpenes and ent-kauran type diterpenes which exhibited significant BACE-1 inhibitory effect [34]. The structure and IC_{50} values of the extracted diterpenes are mentioned in Table 2.2. The serratene type terpenoids isolated from the methanolic extract of *Lycopodiella cernua* (Family: Lycopodiaceae), namely 3*β*,21*β*,29-trihydroxyzerrat-14en-24-oic acid-3*β*-1-(7′-hydroxycinnamate) [IC_{50} value=1.07±0.01 μM], 3*β*,14α,15α,21*β*-tetrahydroxyzerratan-24-oic acid-3*β*-yl-(4′-methoxy-5′-hydroxybenzoate) [IC_{50} value=0.98±0.21 μM], and (2E,4E,6R)-6-hydroxyde-a-2,4-dienoic acid [IC_{50} value=6.91±0.44 μM], showed BACE1 inhibition when analyzed using BACE1 FRET assay [35]. The necrodane terpenoid (2,3,4,4-tetramethyl-5-methylene-cyclopent-2-enone) extracted from the oil of the plant *Lavandula Luisieri* (Family: Lamiaceae) showed inhibition with an IC_{50} value of 120 μg/ml [36]. Terreusterpenes A, B, C, and D, which are 3,5-dimethylorsellinic acid-based meroterpenoids isolated from Aspergillus terrus, a kind of widely distributed common soil fungi, have been shown to be active in inhibiting BACE1 and AchE enzymes. The BACE1 IC_{50} values for the 4 terpenoids were 5.98, 11.42, >40, and 1.91 μM, respectively. Terreusterpene 4 was the most potent and promising BACE1 inhibitor [37]. Three terpenoids isolated from sargahydroquinoic acid, sargachromenol, and sargaquinoic acid extracted from the extracts of Sargassum, a brown seaweed, showed potent inhibitory activity on the BACE1 enzyme with IC_{50} values of 4.4±0.31 μM, 7.0±0.55 μM, and

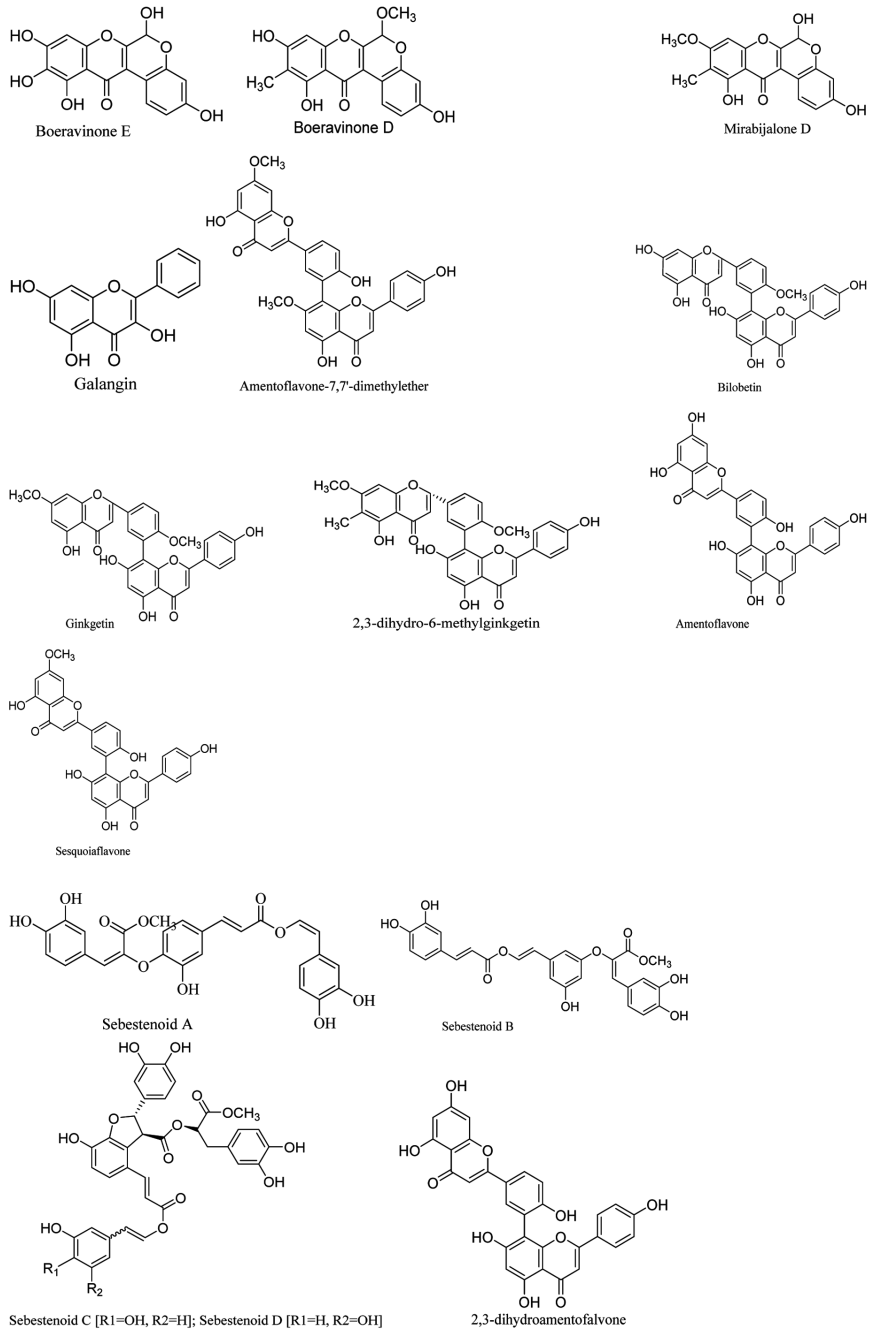
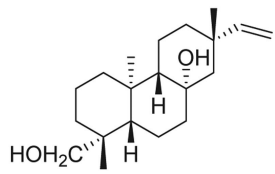
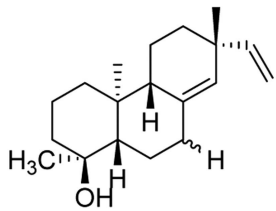
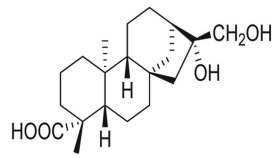
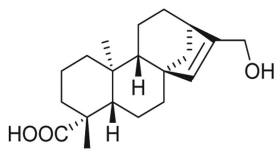
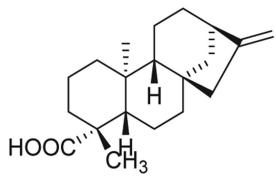
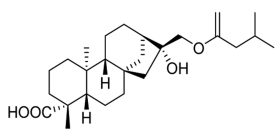
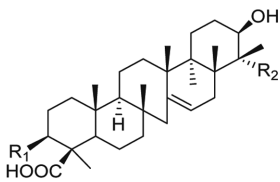


FIGURE 2.6 Structures of flavonoids possessing BACE1 inhibitory activity.

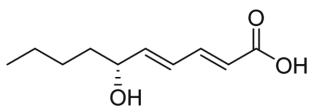
12.1±0.87 μM, respectively [38]. Further studies revealed that sargachromenol, instead of binding with the catalytic dyad of the BACE1 enzyme, bound to allosteric sites and thus proved to be a promising non-competitive BACE1 inhibitor [39] (Figure 2.7).

TABLE 2.2 Diterpenes Evolved from the N-Hexane Fraction of Roots of the Plant *Aralia cordata*

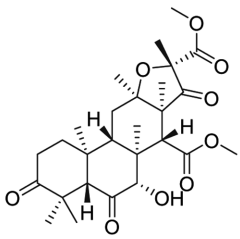
Diterpene Description	Structure	IC50 Value for BACE1 Inhibition
Ent-pimar-15-en-8α,19-diol		92.20 μM
18-no-ent-pimara-8α-14,15-diene-4*β*-ol		41.32 μM
16α, 17-dihydroxy-ent-kauran-19-oic acid		>100 μM
17-hydroxy-ent-kaur-15-en-19-oic acid		23.40 μM
Ent-kaur-16-en-19-oic acid		41.32 μM
16-α-hydroxy-7-isovaleroyloxy-ent-kauran-19-oic acid		Most potent BACE1 inhibitor out of all the extracted diterpenes with IC_{50} value= 18.58 μM.



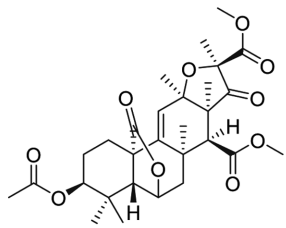
	R1	R2
3b,21b,29-trihydroxyserrat-14-en-24-oic acid-3b-yl-(7'-hydroxycinnamate)	p-hydroxycinnamoyl	CH_2OH
3b,14a,15a,21b-tetrahydroxyserratan-24-oic acid-3b-yl-(4'-methoxy-5'-hydroxybenzoate)	4'-methoxy-5'-hydroxybenzoyl	CH_3



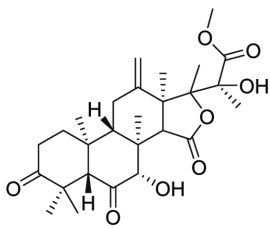
(2E,4E,6R)-6-hydroxyde-a-2,4-dienoic acid



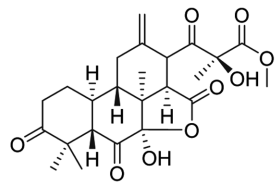
Terreusterpenes A



Terreusterpenes B



Terreusterpenes C



Terreusterpenes D

FIGURE 2.7 Structures of terpenes possessing BACE1 inhibitory activity.

2.4.8 CAROTENOIDS

Crocus sativus L. (Family: Iridaceae) gave rise to 2 active constituents: trans-crocin 4 and trans-crocetin (Figure 2.8), which exhibited anti-amyloidogenic activity in SH-SY5Y cells and decreased BACE1 activity by 20% and 80%, respectively [40].

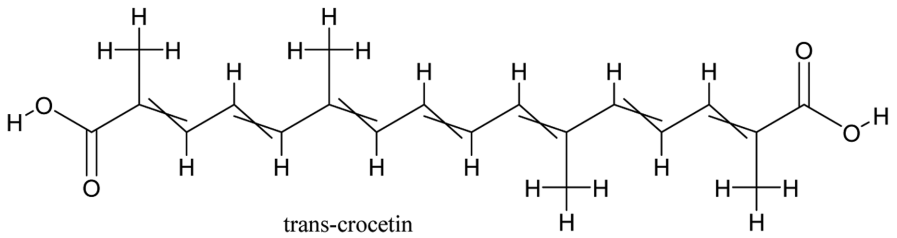


FIGURE 2.8 Structures of carotenoids (trans-crocetin) possessing BACE1 inhibitory activity.

2.4.9 ANTHRAQUINONES

The anthraquinones (Aloenin A,(E)-2-acetonyl-8-(2′-O-feruloxyl)-beta-D-glucopyranosyl-7-methoxy-5-methyl-chromone; 7-O-methylaloeresin A, and barbaloin) derived from *Aloe arborescens* (Family: Xanthorrhoeaceae) were found to inhibit BACE1 in a dose-dependent manner [41] (Figure 2.9).

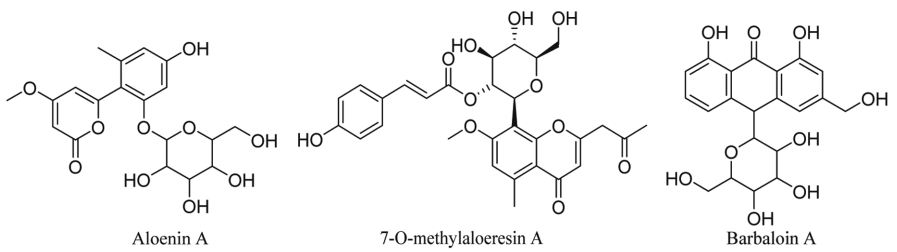


FIGURE 2.9 Structures of anthraquinones possessing BACE1 inhibitory activity.

2.4.10 POLYPHENOLS

Significant BACE1 inhibition was observed when the ethyl acetate fraction of *Camellia sinensis* was evaluated in the BACE1 recombinant assay. Three active catechins were isolated, namely epicatechin gallate, epigallocatechin gallate, and gallocatechin gallate, with their IC_{50} values being 4.5×10^{-6}, 1.6×10^{-6}, and 1.8×10^{-6}, respectively [42, 43]. Researchers evaluated Biophenols extracted from *Olea europaea* for BACE1 inhibition activity using the BACE1 inhibitor screening assay test. The nonflavonoid compounds exerted significant activity, with verbacoside (IC_{50} value = 0.0063 μM) being the most potent one, followed by hydroxytyrosol (IC_{50} value = 0.035 μM), oleuropein (IC_{50} value = 2.76 μM), and caffeic acid (IC_{50} value = 16.67 μM) with the least potency among all. The flavonoid biophenols also showed remarkable inhibition, with rutin (IC_{50} value = 3.8 nM) being the most potent, followed

by luteolin (IC_{50} value = 0.52 μM) and quercetin (IC_{50} value = 0.55 μM) [44, 45]. A biphenolic lignan, 4-O-methylhonokiol, extracted from the bark of the plant *Magnolia officinalis* (Family: Magnoliaceae), was found to downregulate the BACE1 expression in a dose-dependent manner, with the IC_{50} value being 10.3 μM. Curcumin, demethoxycurcumin, and bisdemethoxycurcumin isolated from *Curcuma longa* or turmeric (Family: Zingiberaceae) also exhibited strong BACE1 inhibition when studied in Drosophila melanogaster with overexpressed APP/BACE1 [47, 48]. Moracin derivatives like Moracin M, Moracin P, Moracin O, and Moracin S isolated from *Morus radix* (Family: Moraceae) showed BACE1 inhibition with IC_{50} values of 18.70 μM, 18.15 μM, 36.81 μM, and 3.08 μM, respectively [49]. *Cornus officinalis* gave rise to compounds which showed multi-targeted effects in AD. These caused inhibition of BACE1 and AchE activity. The BACE1 inhibitory activity of these compounds is Cornuside [IC_{50} value = 55.84 μM], 1,2,3-tri-O-galloyl-b-D-glucose [IC_{50} value = 41.20 μM], 1,2,3,6-tetra-O-galloyl-b-D-glucose [IC_{50} value = 20.23 μM] [50] (Figure 2.10).

2.4.11 STILBENOIDS

Stilbenoids extracted from ethyl fraction of *Smilax china* exerted significant BACE1 inhibition. Trans/cis-resveratrol mixture had IC_{50} value of 1.5×10^{-5} M, oxyresveratrol had IC_{50} value of 7.6×10^{-6} M, veraphenol had IC_{50} value of 4.2×10^{-6} M and cis-scirpusin had IC_{50} value of 1.0×10^{-5} M [51] (Figure 2.11).

2.5 PLANT EXTRACTS

The ethanolic extract, hexane fraction, ethyl acetate fraction, and water fraction of the plant *Eisenia bicyclis* (Family: Lessoniaceae) were found to inhibit BACE1 enzyme with IC_{50} values of 0.70±0.21 mg/ml, 1.02±0.11 mg/ml, 0.24±0.08 mg/ml, and 2.12±0.27 mg/ml, respectively [22]. The methanol extract of the rhizome of the plant Curcuma longa and its hexane-soluble fraction, ethyl acetate fraction, butanol-soluble fraction, chloroform-soluble fraction, and water-soluble fraction demonstrated 100% BACE1 inhibition at 2 mg/ml when evaluated using BACE1 fret assay [47]. The methanol extract of *Caesalpinia mimosoides* (Family: Fabaceae) was evaluated in wild-type and APP-overexpressing neurons. It was found that it suppressed the BACE1 activity in the APP-overexpressing neurons. Virtual screening of the extract demonstrated the presence of quercetin-3′-glucuronide, quercetin-3-O-glucoside, clausarinol, and theogallin in the extract as possible inhibitors of BACE1 [45, 52].

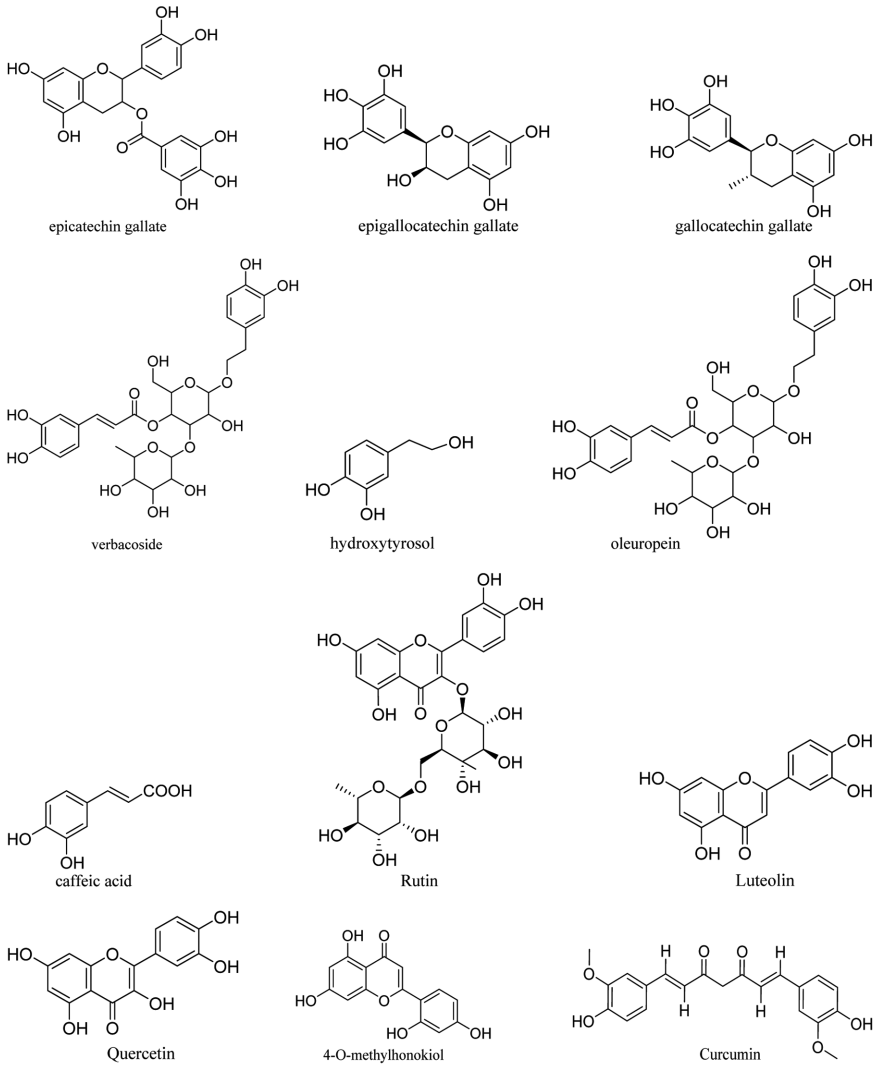


FIGURE 2.10 Structures of polyphenols possessing BACE1 inhibitory activity.

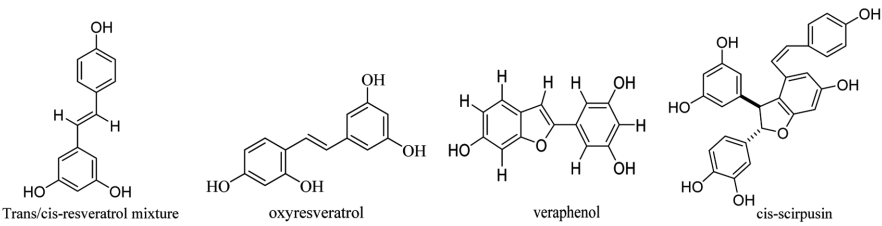


FIGURE 2.11 Structures of stilbenoids possessing BACE1 inhibitory activity.

The embryo extract of the plant Nelumbo nucifera showed potent BACE1 inhibitory effects with an IC_{50} value of 7.47±1.23 μg/ml. The methylene chloride extract was also found to be the most active with an IC_{50} value of 0.02±0.01 μg/ml. Neferine isolated from the methanolic extract of the embryo of the seeds of the same plant also exhibited moderate BACE1 inhibition in an *in-vitro* study [53].

2.6 MISCELLANEOUS PLANT COMPOUNDS WITH BACE1 INHIBITORY ACTIVITY

Asiatic acid extracted from *Centella asiatica* was found to significantly downregulate BACE1 along with the upregulation of ADAM10, IDE levels which aided in the degradation and breakdown of excessive deposited A*β* [54]. Withanolide A isolated from *Withania somnifera* also exhibited similar action when evaluated in primary rat cortical neurons [54].

A phenolic compound, Ferulic acid, was evaluated in the transgenic PSAPP mouse model of cerebral amyloidosis, and behavioral impairment and AD-like pathology were evaluated. The ferulic acid treatment for 6 months reversed the behavioral deficits and spatial working and reference memory. Furthermore, it also led to a reduction in *β*-carboxy terminal APP fragment and downregulated the BACE1 protein stability, lowered neuroinflammation, and oxidative stress.

Resveratrol oligomer separated from the seed extract of *Paeonia lactiflora* (Paeoniaceae) showed remarkable dose-dependent inhibition of BACE1 on baculovirus-expressed BACE1 when analyzed using FRET assay. The IC_{50} values of the isolated compounds are: (–)-7a,8a-cis-ε-viniferin [IC_{50} value=1.29 μM]; trans-ε-viniferin [IC_{50} value=1.85 μM]; cis-ε-viniferin [IC_{50} value=2.21 μM]; trans-resveratrol [IC_{50} value=11.9 μM]; vitisinol C [IC_{50} value=4.01 μM]; vitisinol E [IC_{50} value=19.8 μM]; gnetin H [IC_{50} value=0.34 μM]; suffruticosol A [IC_{50} value=5.99 μM]; and suffruticosol B [IC_{50} value=0.88 μM] [55].

Tannic acid, which is a polyphenol found in various woody and herbaceous plants including raspberries, bananas, wines, and legumes was found to be a natural inhibitor of BACE1 [56].

2.7 CONCLUSION AND FUTURE PROSPECTS

Numerous compounds have been discussed in the chapter, amongst these flavonoids form the richest source of BACE1 inhibitors with significant

efficacy followed by terpenoids. But despite the in-depth knowledge of the pathophysiology of AD and ample research and ongoing clinical trials, the successful cure of the disease hasn't been discovered yet. The multifactorial and complex nature of AD is also a prime cause of clinical failure of drugs and difficulty in crossing the BBB being the second most important factor. Some of the herbal therapies, besides being effective in BACE1 inhibition, have also been explored for their multitargeting potential causing drastic improvement in the symptoms and hallmarks of the disease due to the synergism. Though natural products have been successful in inhibiting the BACE1 enzyme, these can be used as leads which can further be modulated for enhancing their efficacy and multitargeting potential. Although, only after intensive preclinical trials, toxicity studies, pharmacokinetic and pharmacodynamic studies can their toxicity levels, dosage levels, drug-drug interactions be ascertained before these compounds can be extrapolated to clinical use. The practical therapeutic implementation of these compounds still has a long way to go. However, these do harbor significant potential to act as a safe complementary alternative to alleviate the pathogenic markers associated with the deadly disorder and prolong the survival rate of patients suffering from Alzheimer's.

KEYWORDS

- **Alzheimer's disease**
- **amyloid precursor protein**
- **dementia**
- **drug-drug interactions**
- **flavonoids**
- **synergism**
- **β-amyloid plaques**
- **β-secretase enzyme**

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CHAPTER 3

Role of Natural Steroidal Phytopharmaceuticals in the Management of Alzheimer's Disease

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ABSTRACT

Synthetic drugs most commonly manage neurodegeneration, a trademark of Alzheimer's. Phytopharmaceuticals are an emerging area of research as a supplement to these drugs, owing to their lower toxicity and fewer adverse effects compared to synthetic drugs. Steroidal phytopharmaceuticals, especially, are of particular importance in this regard. A modulation of natural neuroprotective steroids present in the brain is an innovative approach to improve patient health. Many herbal drugs containing phytopharmaceuticals like Withanolides, diosgenin, tomatidine, sarsasapogenin, and other steroidal compounds are increasingly being investigated in the treatment of Alzheimer's disease. This chapter focuses on the various natural neuroprotective steroids and the steroidal drugs from natural resources, namely steroidal glycosides, steroidal lactones, phytosterols cucurbitans, steroidal alkaloids, brassinosteroids, and steroidal saponins, that have been explored in literature for the prevention of AD. Also, it focuses on the underlying pathophysiological mechanism involved in neuroprotection and AD.

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3.1 INTRODUCTION

Alzheimer's disease (AD) is categorized as degeneration of brain cells, and the most common type of dementia in elderly patients. It is a neurodegenerative disorder marked by the accumulation of β-amyloid (Aβ)-containing extracellular plaque and tau-containing intracellular neurofibrillary tangles [1]. Aggregate accumulation causes neuroinflammation, synaptic dysfunction, neuronal death, and consequently cognitive decline, typically in the older population [2]. Clinically, the disease manifests as substantial amnestic cognitive impairment, although it can also exhibit as non-amnestic cognitive impairment [3]. Progressive impairment of cognitive and behavioral processes includes impairment of intellectual capabilities, language, loss of motivation, disorientation, and behavioral disorders that significantly impact an individual's everyday activities [4].

Dr. Alois Alzheimer, a German physician and neurobiologist, was the first scientist to report a case of cognitive decline, with histological manifestation of senile plaque and neurofibrillary tangles (NFT) in 1907 [5]. The disease was thereafter named after him in the year 1910 [6].

Age-related diseases have become more prevalent due to the rapidly aging population of developed countries. The incidence of dementia is on the rise in both middle/low-income and high-income countries during the last 50 years due to the rise in average life expectancy. The worldwide occurrence of all-cause dementia is anticipated to rise from 50 million in the year 2010 to 113 million by the end of 2050. However, several high-income countries, such as the United States, the United Kingdom, and France, have reported a slight decline in the occurrence of the disease [7].

3.2 ETIOLOGY OF ALZHEIMER'S DISEASES

Epidemiological studies suggest involvement of various risk factors in the pathophysiology of Alzheimer's, such as heredity, age, head injury, infection, vascular disease, and environmental exposure (trace metals and heavy metals). Age is known to play a major role [8, 9]. Aging is a complex phenomenon. It is an irreversible change that affects various body organs and cellular systems, resulting in a decrease in brain weight and volume, synaptic loss, ventricular expansion in certain locations, as well as the deposition of senile plaques and neurofibrillary tangles [10]. Genetic factors account for 90 to 95% of sporadic Alzheimer's cases [11].

AD is broadly classified into two sub-categories based on age of onset: Early-onset AD or Familial Alzheimer's and late-onset AD or sporadic AD. Familial Alzheimer's is a relatively rare autosomal dominant condition with an early onset (age < 65). Sporadic AD occurs later in life, after the age of 65. Most AD cases are sporadic, caused by genetic predisposition and environmental factors. Both forms can occur in individuals with a family history of Alzheimer's [12].

Genetic factors play a vital role in the progression of AD. Early-onset AD is inherited in an autosomal dominant pattern. Mutations occur in dominant genes such as apolipoprotein E, amyloid precursor protein, presenilin-1, and presenilin-2, and are linked to neurodegeneration [13]. There is a substantial increase in the accumulation of β-amyloid in Early-onset AD. During the pathogenic phase, soluble Aβ oligomers influence synaptic plasticity. All forms of the disease seem to involve amyloid β peptide overproduction and/or impaired clearance, ultimately leading to neurodegeneration, memory loss, and death [11, 14].

Clinical symptoms of AD vary depending on the grade/severity of cognitive impairment. Based on this, it is categorized as mild, moderate, or dementia-stage. In the mild stage, the most common symptom is episodic short-term memory loss. There are early morbid alterations in the hippocampus and cortex, with little functional disability in everyday activities. During the mild stage, patients experience difficulties in everyday activities such as loss of concentration and memory, disorientation, mood swings, and depression [15]. Short-term memory impairment is accompanied by impairment in executive functioning, problem-solving, lack of motivation, judgment, and disorganization, leading to problems with multitasking and abstract thinking. Executive functioning impairment in the early phases varies from mild to substantial [16, 17].

In the moderate stage, further pathological alterations in areas of the cerebral cortex result in progressive memory loss, difficulty recognizing near and dear ones, and dyspraxia. Sleep disturbances, olfactory dysfunction, akathisia, Parkinson-like symptoms, and dystonia occur late in the disease [16].

In the late stage, there is a critical deposition of β-amyloid plaques along with neurofibrillary tangles in the entire cortex area, resulting in cumulative functional and cognitive disability. The patient is unable to recognize their near and dear ones. They experience difficulty in swallowing food and have trouble urinating as well. These complications ultimately lead to the death of the patient [18].

This chapter focuses on different natural steroids that have been explored in the literature for the management of AD. These include both the endogenously occurring neuroprotective steroids as well as exogenous steroids from various plant sources.

3.3 MECHANISMS OF NEURODEGENERATION IN ALZHEIMER'S DISEASES

AD is associated with the destruction of nerve cells in the central nervous system (CNS) through several mechanisms. Various pathological processes are engaged with the mechanism of AD, such as abnormal deposition of Aβ (amyloid β) peptide, accumulation of NFTs, cognitive decline, depletion or insufficient synthesis of neurotransmitters, neuroinflammation, mitochondrial dysfunction, and oxidative stress linked to neurodegenerative diseases [19]. This causes irreversible and progressive memory loss, as well as loss of various cognitive functions. Both environmental and genetic factors play a major role in the pathogenesis of AD. Several hypotheses, including the Aβ hypothesis, cholinergic hypothesis, and tau hypothesis, have been proposed to explain this multifactorial phenomenon based on multiple causative factors [5, 19].

3.3.1 CHOLINERGIC HYPOTHESIS

Cholinergic hypothesis for neurodegeneration establishes the decrease of cholinergic functioning in the cortical and hippocampal regions of the brain as a causative factor for AD. Patients with this disorder have been identified with alterations in choline acetyltransferase and acetylcholinesterase (AChE) activity and reduced acetylcholine (ACh) levels. Furthermore, changes in nicotinic and muscarinic receptor levels in the brain have been identified in AD patients. Aβ also plays a role in disrupting cholinergic neurotransmission, resulting in decreased choline absorption and the release of ACh [20]. Several AChE-selective inhibitors, such as donepezil, dual inhibitors of AChE, galantamine, rivastigmine, and butyrylcholinesterase, are used to treat AD [21].

3.3.2 AMYLOID-B HYPOTHESIS

Accumulation of intracellular NFTs and extracellular Aβ peptide plaques are the two major neuropathological changes in AD (Figure 3.1) [22]. The anomalous β-sheet deposition in CNS is associated with dementia. The

precursor for this peptide is a type-I transmembrane protein called the amyloid precursor protein (APP). It is cleaved by α, *β*, and γ-secretase, to release amyloid *β* and other proteins [23]. APP processing is classified into non-amyloidogenic and amyloidogenic pathways based on its cleavage products. The former pathway involves APP cleavage by α and γ-secretase, while the latter involves proteolytic cleavage by *β* and γ-secretase complex in a sequential manner [24]. This cleavage produces amyloid peptides with different chain lengths including A*β*37, 38, 39, 40, 42, and 43. Among them, A*β*40 and A*β*42 are the most critical A*β* peptides in CNS [25]. An increase in the ratio of A*β*42 to A*β*40 leads to the formation of A*β* amyloid fibril. This results in neurotoxicity which further leads to synaptic dysfunction and neurodegeneration [26]. Furthermore, mutations in genes like PSEN1, PSEN2, and APP; along with other risk factors have been found to affect A*β* deposition and the rapid progression of neurodegeneration [27].

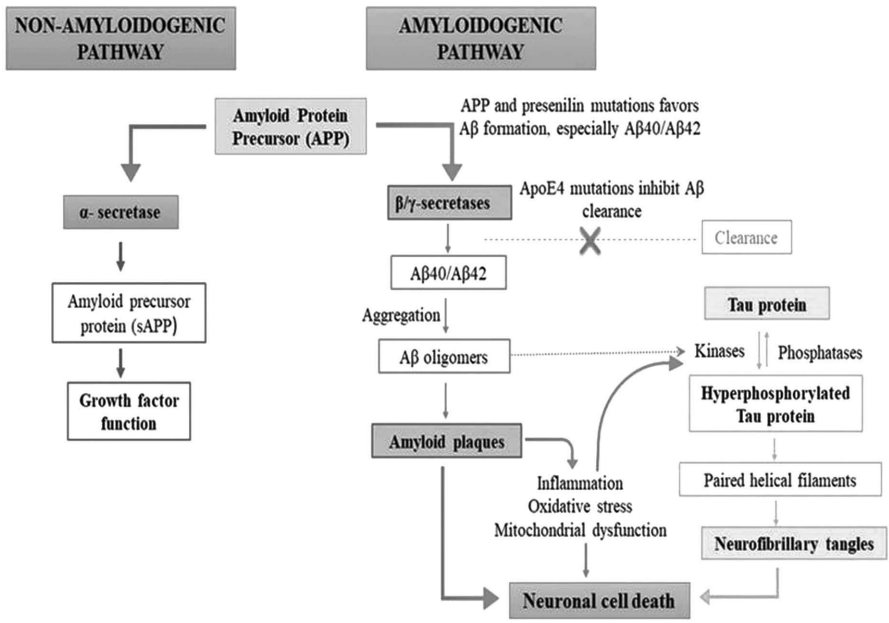

FIGURE 3.1 Mechanism of neuro-degeneration in Alzheimer's disease.

3.3.3 TAU HYPOTHESIS

Tau protein helps to stabilize and regulate microtubules in nerves. However, pathological alterations may cause phosphorylation of tau leading to the

development of insoluble forms which are neurotoxic. This hyperphosphorylated tau protein forms the main component of neurofibrillary tangles found in the brain of patients suffering from AD [28]. The neurofibrillary tangles twist around each other and accumulate in neural perikaryal cytoplasm. These are then called paired helical filaments. This excessive accumulation of hyperphosphorylated tau results in reduced axonal transmission and improper mitochondrial function (mitochondrial fusion and fission), which leads to brain injury [29]. Thus, inhibition of tau protein accumulation is one of the potential approaches for the prevention and treatment of AD [30].

AD can be characterized as increased production and deposition of Aβ, decrease in cholinergic functioning, and the development of neurofibrillary tangles. Therefore, the current drug therapy mainly includes the use of AChE inhibitors, like tacrine, rivastigmine, donepezil, and galantamine. Others such as memantine and N-methyl-D-aspartate (NMDA) receptor antagonists are also utilized. However, these medications often induce adverse effects such as hepatotoxicity, diarrhea, sleeplessness, or illness [31, 32]. Natural products have been considered as an effective and alternative treatment in the management of AD compared to synthetic drugs [33]. Several natural herbal compounds have multifunctional activities which may be suitable for the treatment of AD.

3.4 STEROIDS: A POTENTIAL PHYTOCONSTITUENT FOR ALZHEIMER'S DISEASES

Natural products have recently gained popularity as a supplemental or alternative therapy, owing to their lower toxicity and fewer adverse effects compared to synthetic drugs. Many natural products and phytochemical components, like flavonoids, polyphenols, lignans, tannins, steroids, alkaloids, and triterpenes have shown beneficial pharmacological effects. For instance, anti-amyloidogenic, anti-inflammatory, antioxidant, and anti-AChE activity in the management of Alzheimer's [34].

Steroids, especially from natural origin, are widely explored in this regard. These can be broadly divided into two categories, namely endogenous neuro-protective steroids and exogenous steroids. Natural endogenous steroids are mainly the steroidal chemicals found in the CNS which modulate the neuronal cell life by avoiding excitotoxicity, apoptosis, and the formation of harmful free radicals. Natural exogenous steroids, on the other hand, are the various natural products of plant origin which contain steroidal

phytopharmaceuticals involved in the management of Alzheimer's. These are illustrated in Figure 3.2.

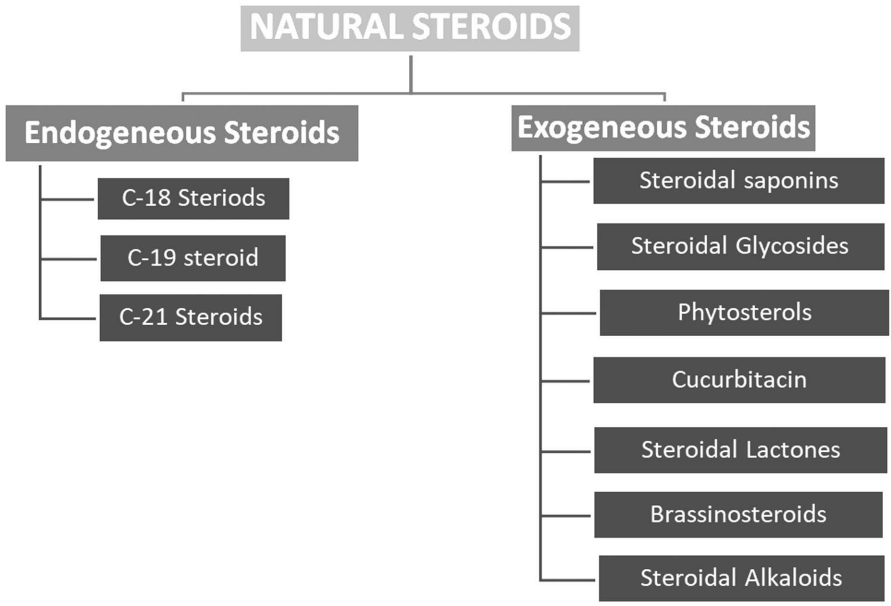

FIGURE 3.2 Classification of natural steroids used in management of Alzheimer's disease.

Endogenous neuroactive steroids (Figure 3.3) are formed via de novo synthesis in the CNS. AD patients show notable alterations in their metabolism and concentration levels in blood, brain, and cerebrospinal fluid (CSF). These steroids are responsible for maintaining the physiological functions in the brain by modulating neuronal excitability and gene expression. They have the potential to target the various neurobiological pathways that are causative factors for neurodegeneration and cognitive impairment. This includes modulation of oxidative stress, reduction of mitochondrial dysfunction, and neuroinflammation [35, 36]. Therefore, exogenous delivery of these agents or a modification of their endogenous production could impart therapeutic benefits before the onset of neurodegeneration.

Exogeneous natural steroids are those natural phytopharmaceuticals which contain steroidal ring in their chemical structure and these compounds have been reported to be useful in management of Alzheimer's.

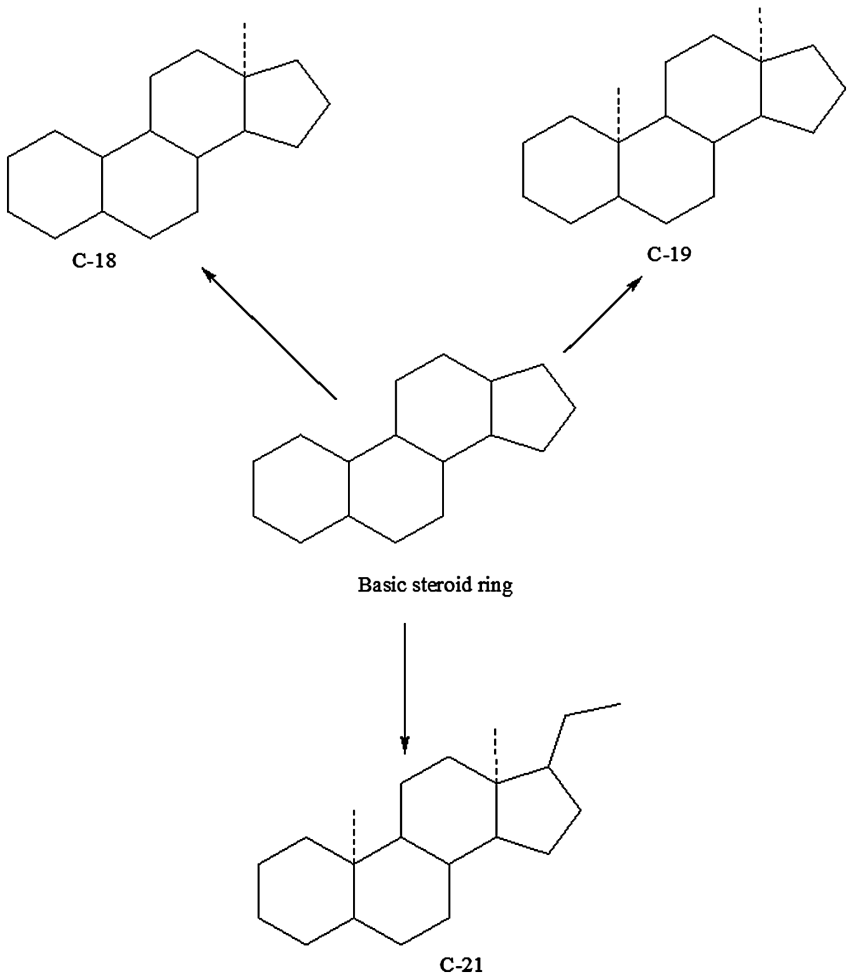

FIGURE 3.3 Endogenous natural steroids.

3.5 NEUROPROTECTIVE EFFECT OF NATURAL STEROIDS IN ALZHEIMER'S DISEASE

Neuroactive steroids are known as neuroprotective steroids as they guard the nervous system from neurodegeneration. These function as protective agents as well as physiological regulators and are produced by steroidogenesis in peripheral glands. The major natural neuroactive steroids are the hormonal steroids namely estradiol, testosterone, pregnenolone, dehydroepiandrosterone (DHEA), DHEA sulfate, tetrahydro deoxycorticosterone,

and allopregnanolone. These promote survival of neurons by activating a variety of mechanisms in the brain. Some of them improve the action of ion channels linked with neurotransmitter receptors, augment antioxidant activity mediated by steroid receptor-independent mechanisms, and regulate cell metabolism and survival through mitochondrial steroid receptor transmission. All of these processes improve neuronal cell life by avoiding excitotoxicity, apoptosis, and the formation of harmful free radicals [37]. The natural neuroprotective steroids can be categorized into various classes namely C-18 steroid (Estradiol), C-19 steroid (DHEA, DHEAs, testosterone, and dihydrotestosterone), C-21 steroids (Progesterone, Allopregnanolone, pregnanolone) based on chemical structures.

3.5.1 ESTRADIOL (C-18 STEROIDS)

Estradiol is a sex hormone, responsible for the growth and development of female reproductive organs and secondary characteristics. Besides this, estradiol is synthesized from steroid precursors inside the brain to exert neuroprotective action. Experimental studies have elucidated that the neuroprotective effect of estradiol is primarily mediated by modulation of cholinergic neurotransmission, decrease in neuronal cell death, and activation of synaptic transmission [38]. Recently, estrogen therapy in experimental autoimmune encephalomyelitis (EAE) rats was shown to lower the levels of pro-inflammatory markers like interleukin 6, interferon-gamma, and TNF-α, and downregulate their receptors. It also improved the levels of TGF-β2 and β3 (transforming growth factor), indicating that estradiol targets the crucial factors involved in the etiology of AD [39]. Another experimental study shows that estradiol also regulates the accumulation of β-amyloid in the brain and therefore protects nerve cells from damage. This was attributed to the role of estradiol in regulating the expression of proteins that are responsible for apoptosis and repression of excitotoxic neuronal death. Additionally, tau protein hyperphosphorylation, a hallmark of AD, is also prevented by estradiol [40].

3.5.2 DHEA AND TESTOSTERONE (C-19 STEROIDS)

DHEA, a C-19 endogenous hormonal steroid, is secreted by adrenal glands and gonads. It is the most abundant circulating hormone in the human body. DHEA is reversibly converted to DHEA sulfate (sulfate ester of DHEA) in the presence of the enzyme sulfotransferase [41]. Additionally, DHEA is converted to testosterone, estradiol, or dihydrotestosterone, and exerts

neuroprotective effects via androgen and estrogen receptors. Recent research has provided enough evidence to support DHEA's therapeutic potential as a neuroprotective steroid, including anti-inflammatory, antioxidant, and anti-apoptotic properties. It also promotes the generation of new neuronal cells and improves neuronal survival in patients with brain injury. DHEA is also gaining a lot of interest for use in experimental animal models of AD because of its potential to improve locomotor and cognitive abilities [42]. Clinical studies have shown that DHEA therapy inhibits the processing of APP via a non-amyloidogenic mechanism, preventing the progressive deposition of toxic Aβ proteins in AD patients. DHEA and DHEAS also reduce gene expression for inflammatory markers like interleukins and TNF-α in experimental animals, as well as inhibit inflammatory gene transcription for CD3 and GFAP. They act as neurotrophic factors, protecting neurons from a variety of damaging events. Both DHEA and DHEAS have neuroprotective properties, which may be achieved by protecting the mitochondria against intracellular Ca^{2+} excess. DHEA is now well recognized as acting as a protective agent against neurodegenerative disorders [4].

Testosterone is a C-19 steroid that is a gonadal sex hormone in the category which plays a vital function in neurogenesis. The new research methodologies show that testosterone has been a strong neuroprotective steroid against neurodegenerative diseases in a variety of animal trials. Testosterone activates androgen receptors present in the CNS, and it easily crosses the blood-brain barrier. It affects brain cells either directly through the androgen pathways or indirectly via estrogen conversion [43]. Recent research has linked low testosterone levels to aging, resulting in memory loss and cognitive function deficits. As a result, exogenous testosterone supplements are advantageous for elderly people. In experimental studies, testosterone showed its protective role within the CNS, which includes N-methyl-D-aspartate excitotoxicity inhibition and elevation of nerve growth factor (NGF) levels in the brain. It also reduces amyloid β deposition and inhibits tau protein hyperphosphorylation. Within the spinal nucleus, testosterone promotes synaptogenesis, plasticity, neurite growth, and neuronal size while also protecting nerve cells from oxidative stress, neuroinflammation, and cell death [4, 44].

3.5.3 PROGESTERONE (C-21 STEROIDS)

Progesterone is a C-21 endogenous steroid and female hormone which is produced in the placenta and ovarian corpus luteum. It is also found in male adrenal glands and male testes. Progesterone and its analogues can be

produced de novo in the brain. Progesterone's neuroprotective actions in males and females mostly include reduction of neurodegeneration, edema, and improved functional recovery. Progesterone includes other neuroprotective actions such as suppression of glial cell excitation in the brain, reduced expression of the inflammatory pathway, reduced excitotoxicity by inhibiting glutamate receptors, and decreased oxidative stress by overexpression of antioxidative enzymes [45]. In experimental models, Progesterone therapy reduces edema, astrocyte deposition in the cortex, and the production of inflammatory mediators such as nuclear NF-kB, interleukins, and tumor necrosis factor-α. It also decreases the activity of iNOS and attenuates the response of reactive macrophage cells. All the evidence shows that progesterone has a favorable effect on inflammatory events by lowering proinflammatory mediators and enhancing the anti-inflammatory response inside the brain [46].

Allopregnanolone is a derivative of progesterone which also plays a vital role in neuroprotection. It improves cognitive functioning and decreases hyperphosphorylation of tau proteins in an experimental study. Furthermore, it reduces apoptotic cell death in NMDA-induced excitotoxicity in human NT2 cell line cultures [47]. Pregnenolone (Figure 3.3) is also a C-21 steroid hormone that is produced in the brain and serves as a precursor for progestogens, glucocorticoids, androgens, estrogens, and mineralocorticoids. Pregnenolone has neuroprotective activities, particularly against neurotoxicity produced by glutamate and β-amyloid protein. It increases polymerization of microtubules, promotes myelination, and stimulates nerve growth factor in clonal mouse hippocampus cells. Dehydroepiandrosterone and pregnenolone serve as agonists of intracellular receptors such as sigma 1 protein, which is primarily involved in memory and learning activities [4, 48].

3.6 THERAPEUTIC POTENTIALS OF PHYTOPHARMACEUTICALS IN THE MANAGEMENT OF ALZHEIMER'S DISEASE

In nature, steroids are classified into nine broad classes, i.e., steroidal saponins, steroidal lactones, steroidal alkaloids, brassinosteroids, cucurbitacins, cycloartanes, phytosterols, and ecdysones. Some of them have been reported to possess anti-Alzheimer activity. These are listed in the subsequent section.

3.6.1 STEROIDAL SAPONINS

These groups of steroids are derived from spirostane and are widely distributed among families like Agavaceae, Dioscoreaceae, Liliaceae,

Scrophulariaceae, etc. They are known for their sapogenins which exhibit a number of therapeutic activities. Some of the plants containing steroidal saponins with reported anti-Alzheimer activity are discussed in subsections.

3.6.1.1 DIOSCOREA

The rhizomes or tubers of the plant *Dioscorea alata* or other species of *Dioscorea* belonging to the family Dioscoreaceae are rich in steroidal saponin named diosgenin [49]. A study reported on memory restoration upon treatment with diosgenin in memory-deficient AD mice model. Biochemical estimation studies suggested that diosgenin works by diminishing β-amyloid plaques as well as neurofibrillary disruption in certain areas of the brain [50, 51]. The plant *Dioscorea alata* or other species of *Dioscorea* belonging to the family *Dioscoreaceae* are rich in steroidal saponin named diosgenin [49].

In another study, the neuroprotective role of Diosgenin against amyloid-beta-induced neurotoxic animal models has been reported in the literature (Figure 3.4). Based on behavioral, biochemical, and histopathological result analysis, it was evident that diosgenin exhibits therapeutic action in the management of AD [52]. Recently, the synthesis of a diosgenin-indole derivative has been reported as a synergistic agent in the management of AD. The study predicted the neuroprotective effect of the synthesized derivative based on the structure-activity relationship. The authors stated that the introduction of an indole ring along with its electron-donating group at the C-5 position is responsible for working effectively against Alzheimer's via different mechanisms such as a decrease in reactive oxygen species and an improvement in cognition [53].

3.6.1.2 GINSENG

The plant belongs to the genus *Panax* and the family Araliaceae. Among all the species of *Panax*, most of the research work has been carried out on three main species, namely: Japanese ginseng (*Panax japonicus*), Asian ginseng (*Panax ginseng*), and American ginseng (*Panax quinquefolius*) [54]. The word Panax was originally derived from the Greek word "*panacea,*" which means healing or longevity. According to folklore, the shape of ginseng root resembles a human body, signifying its immunomodulatory action. Thus, the herb has been used as an adaptogen for several thousand years. The major constituents present in ginseng root are triterpene steroidal saponins, known as ginsenosides or panaxosides. Ginsenosides have four-membered steroid

ring skeletons along with side chain substitution at the C-20 position and sugar moiety or OH group substitution at the C-3 position (Figure 3.3). A total of 30 ginsenosides have been identified, of which the major ones reported in the literature are 20(S)-protopanaxadiol and 20(S)-protopanaxatriol. The basic structural difference between protopanaxadiol and protopanaxatriol is the occurrence of a carboxyl group at the C-6 position in protopanaxatriol. All ginsenosides are known as steroidal saponins as they belong to the steroid family. Earlier classifications indicated that these were also known by the name triterpenoidal saponins or dammarane derivatives [55]. Additionally, ginsenosides are known to be responsible for both stimulatory, inhibitory, and neuromodulator effects on the brain. Some animal studies revealed that ginsenosides prevented scopolamine-induced memory defects. The central cholinergic system mediates the learning and memory process, and it is proposed that ginsenosides increase the reuptake of choline at cholinergic nerve endings, thus known to improve amnesia and nourish neuronal growth. In an *in vitro* study, ginsenosides are reported to rescue neurons affected by ischemic damage and reduce the delayed death rate of neurons observed. Another study showed that ginsenosides enhance the fluidity of synaptosomal membrane and increase the fluidity of cortical cells in experimental animals, which signifies another mechanism for improved amnesic activity. Ginsenosides can modulate the availability of neurotransmitters, thus causing changes in the transmission of neurons. A research study proposed that ginseng inhibits the reuptake of some neurotransmitters such as dopamine, GABA, noradrenaline, glutamate, and serotonin at synapses. Some studies also suggest that ginsenosides bind with the $GABA_A$ receptors in the brain, therefore, it can be a possible mechanism to regulate neurotransmission [54].

3.6.1.3 SHATAVARI

Asparagus racemosus belongs to the genus *Asparagus* and the family Asparagaceae. The genus *Asparagus* is a Greek word which means "stalk" and comprises around 300 species. In Ayurveda, the herb is placed under the category of *Rasayana*, promoting longevity. A series of animal studies explored and reported the nootropic potential of Shatavari. According to the ancient Ayurvedic system of medicine, Shatavari is recognized as a beneficial nervine tonic for a number of neurological disorders. The major steroidal saponins present in Shatavari are sarsasapogenin, shatavarins, racemosides, asparanin A, protodioscin, shatavaroside C, and immunoside [56]. Among all these, Sarsasapogenin is known as a cognitive enhancer and works by

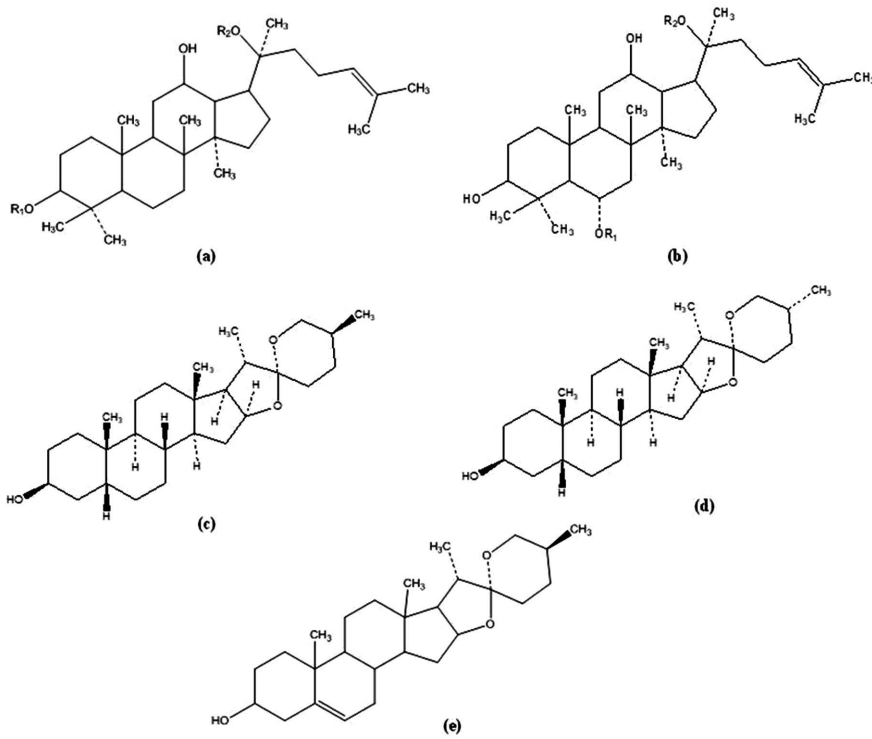

FIGURE 3.4 Structural depiction of some of the steroidal saponins reported for use in management of Alzheimer's disease. (a) 20 (S)-protopanaxadiol; (b) 20 (S)-protopanaxatriol; (c) sarsasapogenin; (d) smilagenin; and (e): diosgenin.

suppressing the overproduction of *β*-amyloid in the brain. Most neurodegenerative disorders occur because of oxidative damage to neurons or neuronal biomolecules and the proliferation of inflammatory processes. In a study, Asparagus ethanolic extract was shown to diminish oxidative damage in certain regions of the brain of experimental animals, suggesting the potential protective role of Shatavari against neurodegenerative diseases [57]. Another pathological mechanism involved in AD is the agglomeration of extracellular *β*-amyloid protein precursor and intracellular oxidized fibrillar protein aggregates; collectively, the process is known as amyloidogenesis. During the normal functioning of the brain, amyloid precursor protein is broken down into soluble peptides by the enzyme α-secretase. Whereas in the case of neurodegenerative diseases such as AD, amyloid precursor protein is broken down into insoluble peptides by the enzyme *β*-secretase. The *β*-amyloid aggregates lead to the formation of toxic macromolecules,

i.e., β-amyloid oligomers and β-amyloid plaques. The β-amyloid oligomers cause increased influx permeability of Ca^{2+} in neurons and ultimately their death. On the other hand, β-amyloid plaques accumulate inside the cell matrix spaces, disrupting the normal interneuronal signaling pathway and showing symptoms of dementia or causing neurodegeneration. Sarsasapogenin, a steroidal saponin from *Asparagus racemosus*, is reported to work through an anti-amyloidogenic mechanism and by inhibiting enzymes such as acetylcholinesterase, butyrylcholinesterase, or monoamine oxidase-B involved in the pathophysiology of AD. Shatavari also acts by releasing certain factors in the brain like brain-derived neurotrophic factor, thus improving the symptoms produced by AD [58]. From the above studies, it is clear that sarsasapogenin is a potent agent for the management of Alzheimer's. A research study based on the structural modification of the lead compound sarsasapogenin reports the synthesis of novel sarsasapogenin-triazolyl hybrids that were found to be effective as anti-Alzheimer agents [59].

3.6.1.4 CHINESE ASPARAGUS

Radix asparagi plant belongs to Liliaceae family. Chinese asparagus is rich in a steroidal sapogenin named smilagenin and in animal studies showed improved memory defects especially in aged rats. The produced activity is due to elevation in diminished levels of muscarinic receptor and its subtype M1 density. In another study, it was reported that smilagenin also elevates the reduced level of brain-derived neurotrophic factor in animal cortical neuronal cell culturing [60].

3.6.1.5 PERSIAN SHALLOT

A. stipitatum plant belongs to Amaryllidaceae family. It contains a steroidal saponin named anzurogenin D; patented for the treatment of cognitive impairment in combination with smilagenin and works by increasing the number of muscarinic receptor subtype M2 in the brain [61].

3.6.2 STEROIDAL GLYCOSIDES

These are most commonly referred to as cardioactive glycosides. Some of the plants reported for management of Alzheimer's are discussed in subsections.

3.6.2.1 SPIKE MOSS

The plant *Selaginella delicatula*, commonly known as spike moss and belonging to the family Selaginellaceae, consists of C-27 steroidal glycosidic compounds, namely Seladelicatulasine – A, B, C, D, E, F, and G, as major active constituents. *In vitro* evaluation of these compounds against cholinesterase, butyrylcholinesterase, and mono-oxidase A and B showed selective inhibitory activities. Among all the constituents, Seladelicatulasine A and F showed the strongest inhibitory activity, indicating their effective role in the management of Alzheimer's [62].

3.6.2.2 VINE SWALLOWWORTS

The plant *Cynanchum auriculatum*, commonly known as vine swallowworts and belonging to the family Apocynaceae, consists of two C-21 steroidal glycosidic compounds, cynsaccatol, and saccatol K, as major active constituents. The neuroprotective effect of these two constituents was assessed using PC12 cell lines. *In vitro* assays such as MTT, Glutathione peroxidase, lactate dehydrogenase, catalase, and superoxide dismutase were used to determine the oxidative stress in cells. Reduced levels of intracellular reactive oxygen species were found, suggesting that the active constituents of the plant could be potential agents for Alzheimer's management, as oxidation is one of the pathological mechanisms of dementia [63].

3.6.2.3 POISON ARROW TREE

The plant *Acokanthera ouabio,* commonly known as poison arrow tree, belongs to the family Apocynaceae and contains a steroidal glycoside named ouabain, also known as G-strophanthin, as an active constituent. In a study, ouabain is taken as a lead compound to find out the therapeutic potential against Alzheimer's, focusing on two mechanisms: increased neural viability in the okadaic-tau hyperphosphorylation neurodegenerative model and nuclear localization of the transcription factor EB. The studies indicated that ouabain shows higher neuroprotective roles in animal models by enhancing the activation of the transcription factor EB and inhibiting tau hyperphosphorylation [64].

3.6.3 PHYTOSTEROLS

Phytosterols, commonly known as plant sterols, are the chief source of phytosterols in dietary vegetables and fruits, containing about 38 to 439 mg/

kg of phytosterols. Unrefined oils including sunflower oil and cottonseed oil contain 4–5 mg/kg of phytosterols [65]. Studies confirm that the blood-brain barrier (BBB) is permeable to phytosterols, which can then accumulate in the brain and might therefore play a crucial part in altering several neural pathways related to neurodegeneration [66].

3.6.3.1 GULFWEED

The seaweed *Sargassum fusiforme*, commonly known as gulfweed and belonging to the family Sargassaceae, contains the active constituent 24(S)-Saringosterol, which exhibits liver X receptor *β*-agonist activity and therefore does not produce any harmful fat deposition effects on the liver. In a neurodegenerative mouse model, it works by inhibiting the *β*-amyloid deposition, hence has a memory-enhancing effect in patients dealing with AD [67].

3.6.3.2 MARSHPEPPER KNOTWEED

The plant *Polygonum hydropiper*, commonly known as marshpepper knotweed, belongs to the family Polygonaceae. It contains *β-Sitosterol*, a dietary phytosterol which is also reported to be present in wheat germ, peanuts, rice bran, corn oil, and soybeans, etc. Chemically, the constituent belongs to the class of stigmastanes. Several *in vivo* and *in vitro* studies have shown that *β*-sitosterol has the highest anti-cholinesterase inhibitory activity. It has been reported that in transgenic animal models, *β*-sitosterol has been proven to restore and improve memory as well as motor coordination. Ethnopharmacological reports state that marshpepper knotweed is beneficial for the management of a number of brain-related disorders, especially neurodegenerative disorders such as Alzheimer's disease. Several animal studies, biochemical studies, and computational studies have been reported in the literature which state that the constituent *β*-sitosterol present in marshpepper knotweed produces anti-Alzheimer effects due to certain properties such as ease of permeation in the brain, anti-AchE enzyme activity, and free radical scavenging property [68].

3.6.3.3 HORNBEAM-LEAVED CROSSBERRY

The plant *Grewia carpinifolia* is a shrub belonging to the family Tiliaceae and is characterized as a neuroprotective herb which contains stigmasterol as the major constituent. Stigmasterol is a dietary phytosterol and is abundant

in most vegetables, legumes, and fruits. Structurally, stigmasterol is a steroid derivative with an alkyl substituent at positions C-22 and C-23, conjugated bonding at positions C-5 and C-6 of the B ring, and a hydroxyl group at position C-3 of the steroid skeleton [65]. Adebiyi et al. [69] isolated bioactive compounds from *Grewia carpinifolia* and tested them for their protective qualities against vanadium-induced brain injury. The findings showed that the bioactive component of this plant (stigmasterol) dramatically improves oxidative stress, motor coordination, and cognitive decline in vanadium-induced neurotoxicity [69].

3.6.3.4 SNAKE JASMINE

The plant *Rhinacanthus nasutus* is commonly known as snake jasmine and belongs to the family Acanthaceae. It is native to tropical Asia. Brimson et al. [70] conducted an experiment to determine the effect of the ethanolic extract of *Rhinacanthus nasutus* on cultured mouse clonal hippocampus cells against glutamate and amyloid-25–35 (HT-22) toxicity. It was discovered that the bioactive phytosterols in the extract possessed strong free radical scavenging capacities [70]. A study on *Rhazya stricta* indicated a strong acetyl-cholinesterase inhibitory action of stigmasterol that was isolated from its fruits, representing its potential role in the prevention of AD [71].

3.6.3.5 DIETARY PRODUCTS

Plant sterols like brassicasterol obtained from dietary sources (nuts, plant oils, sterol-derived dietary products) have a similar structure to cholesterol that facilitates their permeation across the blood-brain barrier (BBB). Chemically, brassicasterol is (22E)-ergosta-5,22-diene with an OH group substitution at the C-3 position, i.e., 3β-sterol. The course of the collection of brassicasterol in cerebrospinal fluid (CSF) results in neuroprotective action against Alzheimer's [72]. Brassicasterol has also been reported to restore the functions of the choroid plexus in AD [73].

3.6.3.6 MACA

The plant Lepidium meyenii, commonly called Maca, belongs to the family Brassicaceae. It is reported as a viable source of neuroprotective phytosterols like campesterol, macamides, and panaxytriol [74].

3.6.4 STEROIDAL TETRACYCLIC TRI-TERPENOIDS/CUCURBITACINS

These are steroidal tetracyclic triterpenoids obtained from diverse plants belonging to the families Cucurbitaceae, Euphorbiaceae, and Cruciferae, and are widely studied for their varied medicinal attributes. The most commonly occurring phytoconstituents are cucurbitacin B and cucurbitacin E, which have been shown to possess anti-Alzheimer potential due to their memory enhancement, elevation in cholinergic and GABA levels, as well as increased neural viability [75].

3.6.4.1 SQUIRTING CUCUMBER

The plant *Ecballium elaterium*, commonly known as squirting cucumber, belonging to the Cucurbitaceae family, is rich in the active constituent Cucurbitacin E. The active constituent in a study was examined for anti-Alzheimer activity in experimental animals. The findings of this study suggest that Cucurbitacin E works by minimizing the tau protein accumulation and therefore helps to increase memory [76].

3.6.4.2 CUCUMBER

The plant *Cucumis sativus*, commonly known as cucumber and belonging to the family Cucurbitaceae, is found to have cucurbitacin, mainly cucurbitacin B, which has an established neuroprotective role against Alzheimer's disease. A study by Uthpala et al. showed that cucumber decreased oxidative stress, decreased neuronal degeneration, and helped in protection against AD [77]. In another study, the neuroprotective role of cucurbitacins from cucumber was established in an intracerebroventricular streptozotocin-induced murine model by demonstrating its anti-inflammatory action, ability to modulate oxidative stress, and alter neurotransmitter levels in the brain [75].

3.6.4.3 PUMPKIN

The plant *Curcubita moscata*, commonly called pumpkin and belonging to the family Cucurbitaceae, contains cucurbitacin B and E. Di Domenico [78] carried out studies on male Wistar rats, where 50–450 mg/kg body weight of extract was administered to assess the memory-enhancing effect. The findings confirmed the same, which was attributed to reduction in oxidative stress (Figure 3.5) and improvement in cholinergic function [78]. In another study, the neuroprotective activity of pumpkin against Alzheimer's was demonstrated by decreasing oxidative stress and reducing neuronal degeneration [79].

3.6.5 STEROIDAL LACTONE

3.6.5.1 ASHWAGANDHA

Withania somnifera, belonging to the family Solanaceae, has long been used in Ayurveda. It is referred to as Ashwagandha, winter cherry, or Indian ginseng and is classified in Ayurvedic literature as a "Rasayana" or rejuvenative tonic. Its root has adaptogenic and energy-boosting effects. It is a nerve tonic and is also recommended for general health improvement. Among its many advantages, one of its most significant functions is its role as a neuro-revitalizing agent for AD. *Withania somnifera* exhibits antioxidant properties that provide protection against oxidative stress and cellular damage brought on by certain inflammatory mediators [80].

There are many phytoconstituents in Ashwagandha, but the main ones are ergostane-type steroidal lactones, such as withanolides (WL) A to Y, withasomniferin-A, dehydrowithanolide-R, withasomniferols A to C, withasomidienone, withaferin A, and withanone, among others. Alkaloids, beta-sitosterol, and sitoindosides VII-X are a few additional components [81, 82].

The anti-Alzheimer's activity of ashwagandha is mostly reported from its root preparations. Root extracts have been reported to act in the hippocampal brain region of stressed rats and exert a neuroprotective effect by decreasing the number of degenerating neurons [83, 84]. Ashwagandha extracts have been shown to act broadly on two pathways: (i) inhibiting stimulation of NF-κB; and (ii) inhibiting production of β-amyloid (Aβ) (Figure 3.5). In a study by Sandhir et al. in 2017 [85], it was proposed that Withanolide-A stimulated the transfer of Nrf-2 inside the nucleus and there upregulated the expression of heme oxygenase-1 (a neuroprotective enzyme). This led to a decrease in apoptotic cell necrosis, restoration of synaptic function, and enhanced antioxidant effect [85]. Identical outcomes were obtained by Baitharu et al. in 2013 [86], where inhibition of hippocampal neurodegeneration and neuroprotective action was observed in Sprague Dawley male rats using *Withania somnifera* (L.) root extract. WL-A activated glutathione biosynthesis and stimulated the production of glutathione. The neuroprotective effect was mediated through AchE activity, Nrf-2 pathway, and nitric oxide (NO) in a corticosterone-dependent manner [86, 87].

Apart from Withaferin A, Withanoside IV and VI have also been reported to show protective action on axons and dendrites of neurons. Other steroidal phytoconstituents isolated from ashwagandha like sitoindosides IX and X have been reported to improve learning and memory enhancement in both younger and older experimental rats [88]. The proposed mechanism for this activity is through modulation of cholinergic neurotransmission [84].

Hannan et al. [89] carried out network analysis on ashwagandha and concluded that the major components of ashwagandha like β-sitosterol, stigmasterol, withanolide A, withaferin A, and withanolide act via targeting several pathways and proteins. The targeted pathways involved are PI3K/Akt signaling, neurotrophin signaling, and toll-like receptor signaling, whereas the targeted proteins include Tropomyosin receptor Kinase B (TrkB), Glycogen Synthase Kinase-3β (GSK-3β), Toll-Like Receptor 2/4 (TLR2/4), and β-secretase (BACE-1) [89]. Exhaustive studies have been carried out on ashwagandha to explore its neuroprotective activity in the management of Alzheimer's disease; these have been tabulated in Table 3.1 and Figure 3.5.

TABLE 3.1 Summarization of the *In-Vivo*/*In-Vitro* Intervention of Ashwagandha for Exploring Anti-Alzheimer's Activity

Ashwagandha Extract/ Phytoconstituent	Study/Animal Model	Effect Observed	References
Sitoindosides. VII–X and Withaferin A in equivalent quantity.	Alzheimer's disease model	Significant reduction in the markers of cholinergic neurotransmitter is observed after two weeks of treatment.	[90]
Withanamides A and C isolated compounds	PC-12 cells and rat neuronal cells.	Reduced cell death. Proposed mechanism of this study indicated that Withanamides A and C attached to β-amyloid and therefore inhibited the formation of fibril.	[91]
Withania somnifera extract	$AlCl_3$ induced AD in rats.	Improvement in biochemical alteration caused by $AlCl_3$. Neuroprotective effect.	[92]
Withaferin-A loaded PLGA nanoparticles.	*In vitro* drug release.	Brain targeted designed Withaerin A nanoparticles was able to exert neuroregeneration action via antioxidant mechanism.	[93]
Semi-purified root extract consisting predominantly of Withanolides and withanosides.	Middle and old aged APP/PS1 AD Transgenic mice.	Restoration of behavioral deficits, inhibition of plaque and Aβ peptides accumulation in the brain was noted. Aβ clearance increased by up-regulation of liver lipoprotein receptor-related protein.	[94]
W. Somnifera fruit extract (250 mg/kg) i.p	*In vivo* mice model.	Withanamides crossed the blood-brain barrier and shown its effectiveness against stress induced brain disorders.	[95]

TABLE 3.1 *(Continued)*

Ashwagandha Extract/ Phytoconstituent	Study/Animal Model	Effect Observed	References
Withanone (WS-2) isolated from root extract.	*In vivo* rodent model.	By inhibition of amyloid β-42 can improve cognitive skill. Withanone attenuated elevated pro-inflammatory cytokines like TNF α, IL-1β, IL-6, MCP-1, NO, lipid peroxidation level. WS-2 affects the β- and γ-secretase enzymatic activity. Significant reversal of decrease in acetyl choline and glutathione activity.	[96]

Aqueous extracts of ashwagandha have also been shown to amplify the level of cognition enhancers and memory improvement agents, i.e., acetylcholine and choline acetyl transferase activity in experimental animals [97, 98].

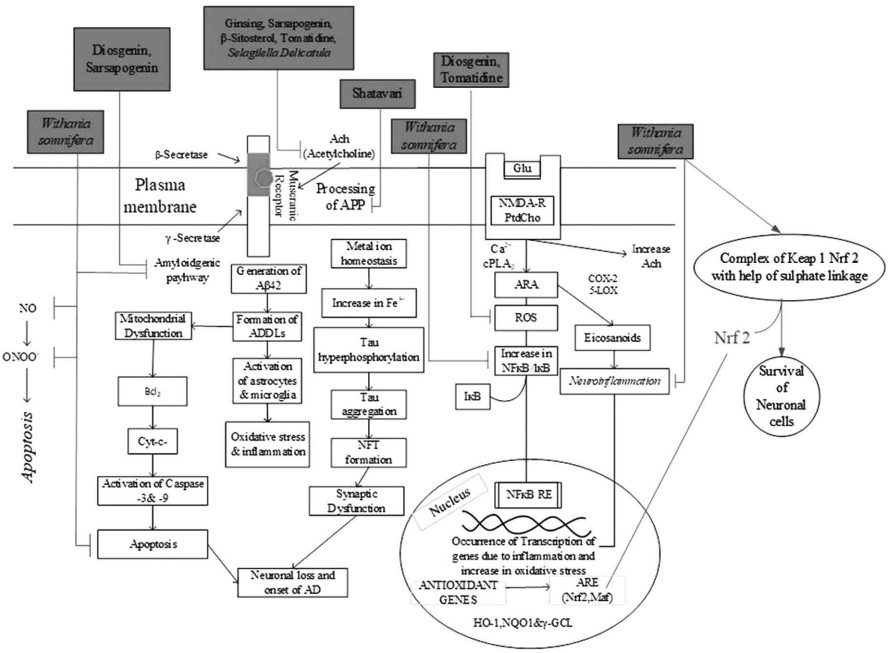

FIGURE 3.5 Diagram illustrating the various pathways for neurodegeration and the potential target sites of various phytosterols.

Abbreviations: APP: Amyloid precursor protein; NMDA-R: NMDA receptor; PtdCho: phosphatidylcholine; ROS: reactive oxygen species; NF-kB: nuclear factor-B; NF-KB-RE: nuclear factor-kB-response element; ARA: arachidonic acid; Glu: glutamate; COX-2: cyclooxygenase-2; and 5-LOX: 5-lipoxygenase.

3.6.6 PLANT HORMONE

Epibrassinolide is a naturally occurring plant hormone commercially available for the growth of hydroponically grown plants. In a cell line culture study, it was found that Epibrassinolide inhibits the enzyme glycogen synthase kinase 3β, therefore preventing cell necrosis. It is proposed that an inhibitor of the glycogen synthase kinase 3β enzyme improves the pathological conditions associated with AD [99].

3.6.7 STEROIDAL ALKALOIDS

This group of steroids consists of a basic nitrogen atom either inside the closed ring or as a side chain substituent in association with the basic steroidal skeleton.

3.6.7.1 TOMATO

The leaves of the plant *Lycopersicon esculentum*, commonly known as Tomato, are rich in tomatine and tomatidine steroidal alkaloids. Both constituents were screened for their neuroprotective effect in a glutamate-induced neurotoxic animal model. The study indicated that they work as antagonists of the cholinesterase enzyme and specifically act on 7-α type nicotinic receptors, with no action on muscarinic receptors. Tomato is also rich in antioxidants, therefore reducing reactive oxygen species which play a major role in the pathogenesis of Alzheimer's [100].

3.6.7.2 CORTICUM

Steroidal alkaloid, 4-acetoxy-plakinamine B, has been isolated from the sponge *Corticum* spp. It bears stigmastane as the basic skeleton. In a study, it was reported that 4-acetoxy-plakinamine B isolated using bioactivity-guided fractionation method from the sponge exhibits strong anti-acetylcholinesterase activity [101].

3.7 CONCLUSION

Herbal drugs are increasingly being experimented in the management of AD. In this regard, steroidal phytopharmaceuticals particularly withanoloids, diosgenin, tomatidine, brassicasteroids have been proved to exert anti-Alzheimer's activity by modulating the major pathophysiological pathways

like inhibition of the β-amyloid pathway, decrease acetylcholinesterase activity, and inhibition of tau protein. Overall, steroidal phytopharmaceuticals have great potential in the management of AD.

KEYWORDS

- **acetylcholinesterase activity**
- **Alzheimer's disease**
- **brassicasteroids**
- **dementia**
- **herbal drugs**
- **neuro degeneration**
- **steroidal herbal drugs**
- **steroids**
- **β-amyloid pathway**

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CHAPTER 4

Potential Role of Terpenes in the Management of Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is the leading cause of dementia, accounting for a significant portion (up to 80%) of dementia cases. Its primary pathological features consist of Aβ plaques, neurofibrillary tangles (NFTs), gliosis, and loss of neurons. In addition, AD is associated with cerebrovascular amyloidosis, inflammation, and significant alterations in synaptic function. However, breakthrough treatments or preventive strategies still elude us, and neurodegenerative diseases remain debilitating and largely untreatable conditions. Therefore, there is a demand for innovative therapies that target alternative sites, along with strategies that would be appropriate for early and continued use, which are probably necessary for the prevention of AD. There is a need for novel therapeutics against alternative targets coupled with approaches that may be suitable for early and sustained use, likely required for AD prevention. A plethora of information exists in the literature on potential compounds of both synthetic and natural origin that have beneficial effects on preventing Alzheimer's disease. A substantial proportion of these substances belong to the terpenoid group. Approximately 55,000 members of terpenes are known to date. They are five-carbon hydrocarbon isoprene polymers and are miscellaneous lipids found in living entities and products that are produced naturally.

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There are four types of terpenes and terpenoids in BVOCs (biogenic volatile organic compounds), namely isoprenes, monoterpenes, sesquiterpenes, and oxygenated hydrocarbons. Numerous *in vitro*, animal, and clinical investigations have demonstrated that terpenes have anti-inflammatory, anxiolytic, antioxidant, analgesic, anticancer, antitumor, neuroprotective, antimicrobial, anti-mutagenic, anti-allergic, and anti-diabetic activities along with others. In this chapter, firstly we summarize the various plants of terpenoids which show an Anti-Alzheimer's effect. Additionally, we also discussed experiments conducted in both controlled environments and in living organisms have shown that terpenes have the ability to alter pathways associated with Alzheimer's disease. These include targeting Aβ and tau pathology, promoting the increase of brain-derived neurotrophic factor (BDNF), mitigating inflammation and oxidative stress, and stimulating the formation of neurons.

4.1 INTRODUCTION

Neurodegenerative diseases are described as progressive degeneration and loss of certain susceptible neurons due to metabolic or toxic disorders [1]. One of the most commonly known neurodegenerative disorders is Alzheimer's disease (AD). Memory loss and other cognitive impairments, along with deterioration in overall functionality, are the major characteristics of AD [2]. It is the primary cause of dementia in elderly people aged 65 years and older worldwide [3]. In the case of AD, a prolonged, progressive disease course starts many years before the development of any clinical symptoms [4]. The pathogenesis of AD includes the cholinergic hypothesis, Aβ amyloid toxicity hypothesis, tau dysfunction hypothesis, vascular hypothesis, insulin hypothesis, and gene mutation hypothesis [5–8]. Among all these hypotheses, the cholinergic, Aβ toxicity, and tau dysfunction hypotheses are mostly studied [9]. The limitations of existing preventative approaches have elevated the necessity of intervention therapies based on natural products rich in antioxidant content. Recently, a lot of attention has been drawn to the therapeutic potential of terpenoids to control the function of neurons and show protective effects against neurodegeneration associated with aging. For the treatment of several types of dementia, including Alzheimer's disease (AD), many secondary metabolites produced from plants have been identified as prospective therapeutic candidates [10]. Chemically, essential oils are terpenes, which make up one of the major groups of secondary metabolites found in plants [11]. This review consists of natural compounds that act as a treatment therapy for Alzheimer's disease (AD), with an emphasis on terpenoids specifically.

Several terpenoids, such as ginsenosides from *Panax ginseng*, ginkgolides and bilobalides from *Ginkgo biloba*, and cannabinoids from *Cannabis sativa*, have shown beneficial effects for AD and were discussed. These terpenoids have the potential to be further developed as AD treatment options [12].

4.2 TERPENOIDS

Terpenoids are the largest class of naturally occurring compounds, often known as terpenes [13]. The word "terpenes" derives from the word "turpentine." Turpentine is the name given to the viscous, pleasantly smelling resin of pine trees obtained from certain pine trees. Turpentine is a fragrant, viscous balsam that is released when the bark and fresh wood of these pine trees are cut [14]. Traditionally, the term "terpene" refers to any naturally occurring compound produced from plants and made up of isoprene subunits [15]. Terpenoids are a diverse group of compounds that are essential for all living organisms. They play crucial functions in numerous biological processes. Terpenoids, like ubiquinone and menaquinone, take part in electron transport chains during respiration. Furthermore, terpenoids, such as bactoprenol in bacteria, hopanoids, and sterols in plants, have a role in the formation and stability of cell walls and membranes. Their existence is essential for the healthy operation and integrity of cellular structures in a variety of organisms [16]. In the past, terpenoids obtained from plants were primarily utilized by humans in the fields of pharmaceuticals, food, and plants [17]. Terpenoids are found in abundance in nature, having varied structures and a wide array of types. Currently, over 50,000 terpenoids have been found in natural sources, the majority of them are extracted from plants [18]. Terpenoids represent a vast and diverse category of naturally occurring compounds. They belong to a class of natural products derived from mevalonic acid (MVA) and contain a number of isoprene (C5) structural units [19]. Terpenoids are terpene derivatives with more oxygen atoms in their structure than terpenes. Terpenoids are mostly produced by plants using the mevalonate pathway, while some terpenoids can also be found in marine creatures [20]. Many *in vivo*, preclinical, and clinical studies affirm that terpenoids have extensive pharmacological properties [21]. Over the last few years, a wide range of research on terpenoids, particularly those derived from medicinal plants, have revealed their role in the field of medicines. They possess a number of biological activities which include protective effects and as a treatment option for tumors, inflammation, bacterial infections, viral diseases, malaria, and cardiovascular diseases, etc. Moreover, some

terpenoids also show effects like insecticidal activity, immunomodulatory, antioxidant, anti-aging, and neuroprotective properties. Terpenoids such as paclitaxel and artemisinin have gained widespread clinical application [22].

4.3 CLASSIFICATION OF TERPENOIDS

Terpenoids are key components of several essential functions of plants such as growth, development, reproduction, and defense mechanisms [23]. Terpenoids share a common feature known as the isoprene chain. Every terpene has an identical, recurring isoprene unit of five carbons. Terpenoids are classified based on the number of isoprenoid units (Table 4.1) in their structure, such as hemiterpenes having one isoprene unit; monoterpenes having two isoprene units, e.g., Pulegone; sesquiterpenes having three isoprene units, e.g., Polygodial; diterpenes having four isoprene units, e.g., Paclitaxel; sesterterpenes having five isoprene units; triterpenes having six isoprene units, e.g., β-Amyrin; tetraterpenes having eight isoprene units, e.g., β-Carotene; Polyterpenes having multiple isoprene units like rubber [24]. Triterpenoids have antidiabetic, antihyperglycemic, and hypoglycemic effects, while diterpenes, triterpenes, and sesquiterpenes have antihelminthic, antiseptic, antibiotic, and insecticidal effects [25]. Studies have revealed that terpenoids possess anti-inflammatory and antioxidant properties, resulting in a decrease in the production of reactive oxygen species (ROS) and malondialdehyde (MDA). They have also been discovered to boost the activity of superoxide dismutase, which aids in the removal of free radicals [26].

TABLE 4.1 Classification of Terpenoids

Sl. No.	Terpenoids	Number of Isoprene Units	Molecular Formula	Examples
1.	Hemiterpene or isoprene	1	C_5H_8	Isovaleric acid, isoprenol
2.	Monoterpenoids	2	$C_{10}H_{16}$	Camphor, carvone, citral, citronellal, citronellol, geraniol, eucalyptol, linalool
3.	Sesquiterpenoids	3	$C_{15}H_{24}$	Humulone
4.	Diterpenoids	4	$C_{20}H_{32}$	Abietic acid, ginkgolides
5.	Sesterpenoids	5	$C_{25}H_{40}$	Andrastin A, manoalide
6.	Triterpenoids	6	$C_{30}H_{48}$	Amyrin, betulinic acid, limonoids, oleanolic acid, sterols, squalene, ursolic acid.
7.	Tetraterpenoids	8	$C_{40}H_{64}$	Carotenoids
8.	Polyterpenoids	>8	$(C_5H_8)_n$	Gutta-percha, natural rubber.

4.4 TERPENOID AS POTENTIAL NEUROPROTECTIVE AGENTS FOR MANAGEMENT OF ALZHEIMER'S DISEASE

4.4.1 GINSENOSIDES

Alzheimer's disease (AD) ranks among the costliest diseases globally due to lack of treatment options. Clinically, AD features include problems in learning and memory, along with the loss of other cognitive and non-cognitive mental functions [27]. Ginseng, obtained from the roots of *Panax ginseng* Meyer (Araliaceae), is a highly popular herbal medicine well known for its extensive therapeutic and pharmacological effects. For centuries, it has been used in East Asian countries including Japan, China, and Korea, serving as a traditional tonic for longer life of individuals [28]. Ginseng is very popular because of its effectiveness in enhancing the immune system, alleviating fatigue, and improving cognitive functions. Its ability to reduce impairment in cognitive functions associated with aging and the risk of dementia is very intriguing from a scientific and public health perspective [29]. Ginseng contains a variety of bioactive substances, such as mineral oils, fatty acids, polysaccharides, and ginseng saponins. Ginsenosides (triterpene saponins) are responsible for the pharmacological effects of ginseng. Since their initial identification by Shibata's group in the 1960s, over 100 ginseng saponins have been identified from 11 different Panax species. Thin-layer chromatography (TLC) was first used to isolate these saponins, and they were given alphabetical names based on the distance they moved on the TLC plate, such as Rb1, Rb2, Re, and continuing [30]. Studies found that glutamate release becomes more rapid in rat cerebrocortical nerve endings by the ginsenosides Rg1 and Rb1. Their beneficial effects are also seen on the central nervous system, particularly on mental processes like memory and learning [31]. Its cognition-enhancing, antidepressant, and anti-anxiety effects have been documented by Shi-Zhen Li in *Ben Cao Gang Mu*, which is the most comprehensive pre-modern herbal text compiled during the Ming Dynasty in China. There is a lot of data regarding its cognitive and neuroprotective effects. In one study by Li and colleagues, the therapeutic effect of GP and AD along with its correlation with the PI3K/Akt was investigated aiming to uncover the underlying mechanism of ginseng's neuroprotective effect. It was found that GP improved memory ability and reduced the content of $A\beta_{1-42}$ and p-tau in AD rats, and the neuroprotective effects were partially mediated by the activation of the PI3K/Akt signaling pathway [32]. Shin and colleagues [33] investigated the role of Red Ginseng Attenuates Aβ-Induced Mitochondrial Dysfunction and Aβ-mediated Pathology in an Animal Model of Alzheimer's Disease. The

study's findings indicate that the administration of RGE (presumably referring to Red Ginseng Extract) effectively inhibits gliosis (reactive changes in glial cells) and neuronal loss in transgenic mice that overexpress Aβ, which is associated with Alzheimer's disease. These results suggest that RGE, with its anti-mitochondrial properties, may contribute to the reduction of neuroinflammation and neurodegeneration within the AD brain [33] (Figure 4.1).

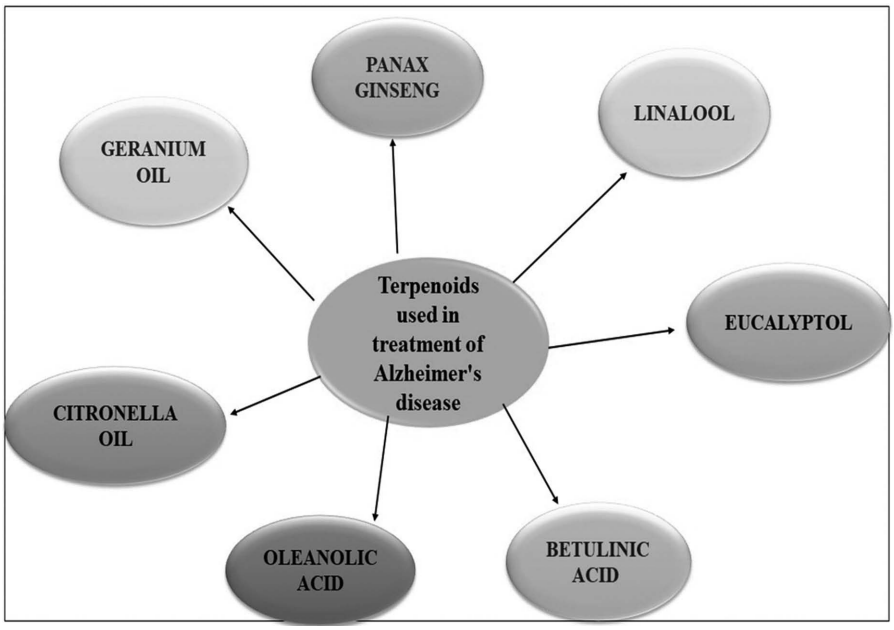

FIGURE 4.1 Terpenoids used in treatment of Alzheimer's disease.

4.4.2 LINALOOL

The monoterpene alcohol linalool ($C_{10}H_{18}O$), also known as 3,7-dimethyl-1,6-octadien-3-ol, is a common component of plant essential oils, mainly lavender and coriander [34]. Linalool is an unsaturated monoterpene alcohol and has a distinctive aroma which is light and refreshing, floral-woody, with a faint citrusy note [35]. In Indian medical systems, linalool is a monoterpene antioxidant found in volatile oils of many aromatic species. Strong antioxidant properties found in linalool enable it to scavenge ROS produced by numerous toxins [36]. It's interesting to note that several species producing linalool have long been used in folk medicine and aromatherapy to treat a wide range of acute and chronic illnesses by minimizing their symptoms [37]. A number of prior

studies have demonstrated the neuroprotective effect of linalool, which mitigates cognitive impairment and has a protective action against brain damage induced by Aβ in transgenic mouse models of Alzheimer's disease. In a study conducted by Sabogal-Guáqueta and colleagues [38], it was reported that the oral administration of linalool (25 mg/kg) in elderly 3xTg-AD mice resulted in a delay in cerebral amyloidosis, including the deposition of amyloid and abundance of β-amyloid peptide. Studies reported that linalool administration can potentially prevent age-related cognitive impairments and the accumulation of β-amyloid in 3xTg-AD mice [38]. Additionally, IL-1β and its downstream components, p38 MAPK, COX-2, and iNOS, were downregulated by linalool therapy, which decreased inflammatory indicators. Linalool has been shown to lower the expression of TNF-α, IL-6, iNOS, and COX-2 in the liver and serum by preventing NF-kB activation [39]. Yuan and colleagues demonstrated that by reducing the generation of free radicals and the inflammatory response, linalool protects against the neurotoxicity of Aβ. Consequently, it is anticipated that linalool will be employed as a preventative or treatment drug for AD [40]. Xu and colleagues [41] demonstrated that the neuroprotective effects of linalool may be due to alleviating apoptosis and oxidative stress caused by Aβ, depending on the induction of the Nrf2/HO-1 pathway. Linalool successfully reversed the cognitive impairment caused by Aβ1-40 in mice [41]. Furthermore, in hippocampal slices, linalool showed its capacity to guard against NMDA-induced excitotoxicity. By maintaining and restoring mitochondrial activity, linalool is thought to have neuroprotective benefits in both *in vitro* and *ex vivo* animals. Linalool also enhances the efficiency of the mitochondria in glutamate-stimulated HT-22 cells. These results suggest that linalool may be therapeutically useful in the treatment of neurodegenerative disorders marked by mitochondrial collapse and the subsequent generation of reactive oxygen species (ROS). This is explained by the fact that it has a positive effect on preserving mitochondrial integrity and that it can reduce oxidative stress [42]. Future research is needed to determine whether linalool lowers the Aβ42-stimulated inflammatory response via regulating the Nrf2/HO-1 pathway and NF-κB activation. Furthermore, alterations in the expression levels of inflammatory mediators TNF-α, IL-1, and PGE2 in AD models should be investigated.

4.4.3 EUCALYPTOL

1,8-Cineole is a naturally occurring monocyclic monoterpene ether (oxide) (1,3,3-trimethyl-2-oxabicyclo[2,2,2]octane) with an aromatic and camphor-like odor found in essential oils of various plant species like *Eucalyptus globulus,*

Eucalyptus polybractea (95% of 1,8-cineole), *Helichrysum gymnocephalum* (47.4% of 1,8-cineole), *Zingiber chrysanthum* (42% of 1,8-cineole), *Rosmarinus officinalis* (43.7% of 1,8-cineole), and many more, with the important natural source being eucalyptus essential oil [43, 44]. Eucalyptol is one example of a lipophilic compound that can alter intracellular lipids and improve penetration of drugs [45]. For transdermal medication delivery, eucalyptol has been used in a lipid-based microemulsion method. Rat and human liver microsomal P450 enzymes metabolize eucalyptol to 2-exo-hydroxy-1,8-cineole, which is then excreted in the urine [46]. Also, eucalyptol is able to cross the blood–brain barrier and may have an immediate impact on receptors and enzymes in the brain. Eucalyptol is positioned as a potentially important therapeutic agent for treating chronic disorders due to its anti-inflammatory and antioxidant effects, as well as its physicochemical qualities [48]. Due to its biological properties, it possesses a therapeutic role against Alzheimer's disease. Khan and colleagues [49] demonstrated the anti-inflammatory role of eucalyptol to ameliorate the cholinergic dysfunction of the cells treated with Aβ (25–35). It was found that eucalyptol successfully reduced the mitochondrial membrane potential, ROS, and NO levels in Aβ (25–35) treated cells. Eucalyptol also lowered the levels of proinflammatory cytokines TNF-α, IL-1β, and IL-6 in Aβ (25–35) treated cells. Moreover, eucalyptol was also successful in decreasing the expression of NOS-2, COX-2, and NF-ƙB [49].

4.4.4 BETULINIC ACID

3-Hydroxy-lup-20(29)-en-28-oic acid, also called Betulinic acid (BA), is a pentacyclic lupane-type triterpenoid that is commonly present in plants [50]. Birch bark has been used for generations in traditional medicine as it contains BA as an active ingredient [51]. BA is mainly obtained from popular medicinal plants like the birch tree (*Betula* sp., Betulaceae). This substance has also been found in various species which belong to the families *Paeonia* (Paeoniaceae), *Ziziphus* (Rhamnaceae), *Diospyros* (Ebenaceae), *Syzygium* (Myrtaceae). Both the compound's free aglycon form and its glycosylated derivatives can be simply extracted directly from these plant sources using a variety of solvents, with dichloromethane being the most popular choice [52]. Due to its biological and pharmacological actions, which include anti-inflammatory, antimalarial, antibacterial, anthelmintic, antiviral, antidiabetic, and antioxidant properties, cancer-fighting properties, and HIV, BA has recently attracted a lot of interest among these substances [53]. In spite of its poor solubility in aqueous environments, BA has the advantage of being able to produce a variety of derivatives

with a number of benefits [54]. Both traditional Ayurvedic medicine (for the treatment of neurological diseases) and modern medicine (for various carcinomas) have extensively used BA therapeutically. Its ability to cross the blood-brain barrier, safety at dosages more than 500 mg/kg, and extensive elimination half-life make BA an ideal substance for diagnosing central nervous system (CNS) disorders [55–57]. In a study conducted by Sarkaki and colleagues [58], it was shown that Betulinic acid could potentially contribute to the treatment of Alzheimer's disease by preserving microcirculation, reducing inflammation, and boosting the expression of BDNF (Brain-Derived Neurotrophic Factor). These effects were especially prominent when maintaining a molar ratio of 1:4 between Aβ (Amyloid-beta) and BA (Betulinic acid) [58]. Kaundal and colleagues [59] showed that BA protects rat brain from Streptozotocin-induced neuronal damage by working through various mechanisms (anti-inflammatory actions and antioxidant actions), and this substance could be used to prevent cognitive decline brought on by neurodegenerative diseases, including AD [59]. Ruhal & Dhingra [60] provided pharmacological evidence showcasing the neuroprotective and memory-enhancing effects of betulinic acid in both aged rats and rats with scopolamine-induced amnesia. These effects are likely attributed to the compound's anti-acetylcholinesterase and antioxidant activities [60]. To better understand the precise downstream signaling pathways that contribute to the neuroprotective action of betulinic acid, additional research is still required.

4.4.5 OLEANOLIC ACID

The pentacyclic triterpenoid molecule oleanolic acid (OA), also known as 3-hydroxyolean-12-en-28-oic acid, is widely distributed among a variety of plants [61], occurring naturally as a free acid or as an aglycone of triterpenoid saponins, and can often be found with its isomer, ursolic acid [62]. OA is a hard-hydrophobic compound, practically insoluble in water (1.748 µg/L). It is commonly extracted from plants using organic solvents such as methanol, ethanol, ethyl acetate, 1-butanol, diethyl ether, or acetone. Numerous reports have documented the isolation and purification of this triterpene from various plants and herbs. Pharmacological research has explored its beneficial effects, bioavailability, and toxicity, while clinical applications of OA have focused on its use in preventing various pathologies, particularly chronic disorders where oxidative stress and inflammation play significant roles [63]. Oleanolic acid (OA) was found to have a protective effect in a study

by Guo and colleagues [64] by increasing the viability of N2a/APP695swe cells and decreasing apoptosis, caspase-3 activity, reactive oxygen species (ROS) levels, and amyloid-beta (A) content. STC-1 and UCP2 expression were regulated to mediate these effects [64]. In another study, Wang and colleagues [65] found that oleanolic acid (OA) could prevent memory loss brought on by amyloid-beta in rats with Alzheimer's disease (AD). OA had a protective effect during the course of the therapy by protecting synaptic integrity and regaining synaptic plasticity. This was accomplished by upregulating the expression of the proteins NMDAR2B, CaMKII, and PKC in the postsynaptic density (PSD), lowering the concentration of calcium in the synaptic cleft, and strengthening the inhibited long-term potentiation (LTP) brought on by the injection of Aβ25–35. Additionally, OA increased the expression of the proteins BDNF, TrkB, and CREB, which may help explain how it corrects learning and memory deficiencies [65]. When activated by lipopolysaccharide (LPS), microglia exhibit inflammatory and oxidative responses that OA has been shown to ameliorate [63]. Oleanolic acid (OA) improves cognitive deficits in APP/PS1 mice by enhancing neurogenesis in the hippocampus. This effect is achieved through the activation of the Wnt/GSK-3β/β-catenin pathway [66].

4.4.6 CITRONELLA OIL

Geraniol (GE), with the chemical formula $C_{10}H_{18}O$, is an acyclic monoterpene alcohol. Trans-geraniol and Cis-nerol are the two isomers which combine to form "geraniol" that is sold commercially [67]. Geraniol can be obtained by extracting it from the essential oils of various aromatic plants, namely *Cinnamomum tenuipilum* Kosterm (Lauraceae), *Valeriana officinalis* L. (Caprifoliaceae), *Phyla scaberrima* (Juss. Ex Pers.), *Perilla frutescens* var. *hirtella* (Nakai) and *Makino* (Lamiaceae) [68]. Geraniol is widely utilized in the commercial industry as a fragrance compound for cosmetic and household products. It has a distinctive and alluring perfume that people prefer and is often described as sweet, floral, reminiscent of roses, and accompanied by a subtle citrus fruit note. Studies have identified geraniol in 76% of the tested deodorants, 41% of detergents and cleaners, and 33% of cosmetics formulated with natural ingredients [69]. Recent research has revealed that GE has a number of pharmacological characteristics, including anti-inflammatory, antimicrobial, and antitumor activities through its ability to modulate multiple signaling pathways involved in various biological processes. GE (presumably referring to geraniol) shows promise as a potential candidate for drug

development [70–73]. In a study conducted by Rajendran et al. [74], it was demonstrated that GE possesses potent antioxidant activity and effectively mitigates hippocampal injury induced by D-galactose *in vivo*. This neuroprotective effect is attributed to the activation of the PI3K/Akt/Nrf2 pathway, which leads to a reduction in apoptosis and oxidative stress. Consequently, GE contributes to alleviating cognitive dysfunction and reducing neurological deficits in mouse models of D-galactose-induced aging [74]. Geraniol has been shown by Seifi-Nahavandi et al. [75] to reduce oxidative stress and neuro-inflammatory-mediated cognitive impairment in a mouse aging model produced by D-galactose. By exhibiting anti-plaque, antioxidant, and neurogenesis actions in both therapeutic and protective modes, geraniol administration shows significant potential in preventing AD. In addition, it has been demonstrated that geraniol can disaggregate amyloid fibrils that have already formed [75]. Therefore, additional research is necessary.

4.4.7 B-CARYOPHYLLENE

β-Caryophyllene (BCP), also known as trans-(1,9)-8-methylene-4,11,11-trimethylbicycloundec-4-ene, is a bicyclic sesquiterpene that can be found in various plant foods. It is commonly present in herbs and spices such as oregano, cinnamon, pepper, cloves, basil, lavender, rosemary, and caraway. Additionally, it is also found in lemon balm, hops, and certain plant species like *Croton campestris, Ocimum gratissimum, Murraya paniculata L.,* and *Cannabis sativa*. BCP is one of the primary constituents found in the essential oils derived from these plants [76]. *β*-caryophyllene has analgesic, antioxidant, antibacterial, and anti-inflammatory effects and is a volatile molecule with a low water solubility [77, 78]. BCP is a member of the cannabinoid family, which includes compounds that act as ligands for cannabinoid receptors found in the body. The two main cannabinoid receptors are CB1-R and CB2-R, which are G protein (protein binding GTP)-coupled metabotropic receptors. These have a role in regulating neurotransmitters that are responsible for maintaining energy balance, immune responses, and metabolism within the organism [79]. Due to its low water solubility, *β*-caryophyllene has limited absorption into cells when exposed to an aqueous environment such as biological fluids. However, by using liposomal formulation methods, the problems brought on by its limited water solubility can be resolved. These techniques involve encapsulating *β*-caryophyllene within liposomes, which are lipid-based vesicles. By employing liposomal formulations, the bioavailability of *β*-caryophyllene can be increased, resulting in improved

cellular uptake and the desired biological effects [80]. Growing data indicates that -caryophyllene protects neural tissues by activating CB2 receptors in the cannabinoid pathway [81, 82]. Different parts of the brain, including the retina, striatum, cortex, hippocampus, amygdala, cerebellum, and brainstem, express cannabinoid receptors, including CB2 receptors. They are also present in immune cells and the pain-related pathways of the peripheral nervous system. Cheng and colleagues conducted a study demonstrating that the sesquiterpene -caryophyllene produces anti-inflammatory effects by activating CB2 receptors and the PPAR pathway. They suggest that by utilizing *β*-caryophyllene's therapeutic potential, it might be a viable substance for the creation of new therapeutic medications intended to treat Alzheimer's disease (AD) [83]. IL-23 is the cytokine most closely associated with mouse aging. Hippocampal-dependent working memory age-related cognitive loss appears to be reversed by BCP, which lowers the cytokine IL-23, a member of the IL-12 family. In another study, a standardized black pepper seed extract containing *β*-caryophyllene was found to improve memory by regulating brain-derived neurotrophic factor and MAPK proteins [84]. BCP seems to be a promising medication for reducing the effects of aging by inhibiting the IL-12 cytokine family [85].

4.4.8 GERANIUM OIL

Pelargonium graveolens is a fragrant and hairy herbaceous shrub with a rose-like scent. Though it originated in various parts of southern Africa, it is currently produced and cultivated all over the world. There are over 270 distinct species in the *Pelargonium* genus, which belongs to the Geraniaceae family. Only four of the 25 *Pelargonium* species are crucial for the production of essential oils. The four essential oil species are *P. capitatum, P. graveolens, P. odoratissimum,* and *P. radens* [87]. Citronellol, geraniol, and citronellyl formate were the three most prevalent volatile compounds in the *P. graveolens* essential oil [88]. Essential oils and hydrosols from *P. graveolens* are strong antioxidants and have the potential to treat cancer, dysentery, heavy menstrual flow, inflammation, hemorrhoids, and other conditions [89, 90]. Due to its antioxidant properties, it also shows beneficial effects against Alzheimer's disease. A study revealed that the essential oil of *Pelargonium graveolens,* which has strong antioxidant characteristics, can protect the hippocampus from the harmful effects of MET (methamphetamine) by reducing oxidative damage and improving memory [91].

4.5 CONCLUSION AND FUTURE DIRECTION

As one grows older, one is challenged with a number of age-related diseases; particularly those of the brain, of which Alzheimer's disease is the most prevalent. Terpenoids exhibited promising efficacy in the therapy of Alzheimer's disease. Several studies have found that terpenoids like ginsenoside, linalool, eucalyptol, betulinic acid, oleanolic acid, and geraniol can help to improve the pathological hallmark of cognitive impairment such as neuroinflammation, oxidative stress, and beta-amyloid deposition. These substances have shown potential therapeutic benefits against Alzheimer's disease (AD) when their biological activities have been evaluated using *in vivo* animal experiments and *in vitro* cell-based tests. Their efficiency in clinical settings remains a topic of debate. Clinical studies should be carefully planned to include multiple racial populations, various levels of dementia severity, and various dosing schedules of the biologically active substances to address this. Such factors would contribute to a more thorough comprehension of the therapeutic effectiveness of these substances in the treatment of AD.

While further research is required to elucidate their mechanisms of action and potential side effects, terpenoids offer a promising avenue for developing new therapeutic agents for Alzheimer's disease. Their potential as natural products that can be easily extracted from various plants makes them attractive for drug development. Overall, terpenoids represent a promising approach to treating Alzheimer's disease and improving the life of affected individuals.

KEYWORDS

- **Alzheimer's disease**
- **betulinic acid**
- **dementia**
- **methamphetamine**
- **natural products**
- **terpenes**
- **terpenoids**
- **therapeutic agents**
- **therapeutic effectiveness**

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CHAPTER 5

Anti-Apoptotic Natural Products for the Management of Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD), an age-related neurodegenerative disorder, is the most common form of dementia. It is characterized by the degeneration of neurons, cognitive impairments, and loss of memory. The underlying mechanism of the disease is not well defined; however, the critical pathological features affecting AD patients include apoptosis, amyloid plaques (Aβ), neuronal neurofibrillary tangles (NFT), increased oxidative stress, and decreased levels of acetylcholine due to hydrolysis by acetylcholinesterase (AChE). Apoptosis (the programmed cell death) is a typical part of neurodegeneration in AD. It begins via activation of pro-death proteins such as Bax and Bak, activation of caspases, release of cytochrome c, loss of membrane integrity of intracellular organelles, and eventually cell death. Several approaches that block the apoptotic pathways would prevent or delay the neurodegenerative processes. Therefore, the discovery and development of drugs with a multitargeted approach for the management of AD is still a challenge for many researchers. In this context, the exploration of alternative therapies involving various bio-actives from natural products possessing

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antioxidant, anti-apoptotic, and anti-amyloidogenic activities is an important step towards drug discovery for the management of AD. This chapter discusses the role of various natural products with neuroprotective potential, antioxidant activities, and gene-regulating roles that attenuate apoptosis-associated brain cell death. This will provide useful information for various research groups working in this area for the development of potential novel drugs to manage AD.

5.1 INTRODUCTION

The most common chronic neurodegenerative disease, Alzheimer's disease (AD), was first identified by Dr. Alois Alzheimer in 1906 [1] and now affects more than 6 million individuals in the US and over 50 million people globally [2]. As a neurological condition, AD slowly and irreversibly erodes memory, cognition, and finally the capacity to carry out everyday activities, necessitating full-time care. Although it can affect persons of any age, it is most prevalent in those over 65 years of age [3]. The largest risk factor for AD is deemed to be age. This disease affects about 3% of those in the 65–74 age group, 17% of those in the 75–84 age group, and 32% of those in the 85 plus age group [4, 5]. The Centers for Disease Control and Prevention (CDC) lists Alzheimer's disease (AD) as the 6th leading cause of death in the US, but given that it is the most common cause of dementia in older adults. AD may be ranked third among the leading causes of death for seniors, just behind cancer and heart disease [6].

The hallmarks of this disease are thought to be aberrant deposition of insoluble β-amyloid peptide (Aβ) and the build-up of neurofibrillary tangles (NFTs) of phosphorylated-tau protein in neuronal cytoplasm, which leads to atrophy and neuron death (Figure 5.1) [7]. These neurodegenerative alterations have been connected to a number of molecular processes, including aberrant ubiquitination, calcium homeostasis collapse, oxidative stress, neuroinflammation, and neurotransmitter depletion or inadequate synthesis [8]. The result is a loss in learning capacity and other cognitive skills due to damage of the neurons and synapses involved in memory processes [9].

There are just five medications that have been approved by the FDA to treat AD, in contrast to the disease's high prevalence: rivastigmine, galantamine, donepezil, memantine, and memantine combined with donepezil. Furthermore, none of these medications can stop, reverse, or even just moderate the

neuronal loss and degeneration that underlies AD symptoms and renders the condition deadly. Together with the physical, emotional, sociological, and healthcare-related effects of AD, these mostly unmet medical needs have made it difficult for researchers to fully comprehend this difficult disease and develop more efficient management strategies. Massive attempts have been made to pinpoint the underlying causes of this condition and find disease-modifying treatments that can slow the progression of AD [10].

Numerous bioactive chemicals with complex structures and new pharmacological effects are produced in large quantities by natural sources, such as plants, animals, microorganisms, and the marine environment [11]. Natural products and their separated components have been thoroughly researched as one of the main sources of drug discovery to create more potent medications for the treatment of AD [12]. Rivastigmine is a semi-synthetic derivative of a natural substance called physostigmine, as is the cholinesterase inhibitor galantamine [13, 14]. As they have several simultaneous target approaches, mixtures or extracts of natural products may have advantages over individual natural substances. Given the complexity of AD's pathogenesis, this could be a unique therapy option [15]. According to growing data, AD patients may experience cognitive improvements from herbs or herbal formulations as well as combinations made from other natural sources [12]. As a result, many natural sources and their extracts are widely used in AD patients and animal models [16–18].

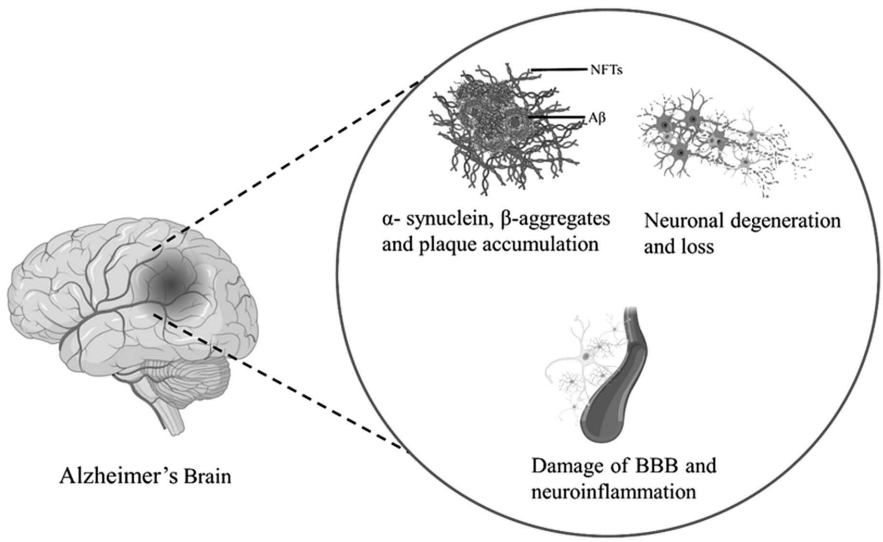

FIGURE 5.1 Various pathways in Alzheimer's affected brain.

5.2 APOPTOSIS AND AD

The word "apoptosis" is derived from the Greek word "*apoptosis*," which means "dropping of petals from a flower" and is related to the development of apoptotic bodies and the wearing off phenomena from the cell. Karl Vogt first detected dying cells in toads in 1842, which led to the discovery of programmed cell death. A scientific upsurge in the field ensued after John Kerr, Andrew Wyllie, and Alastair Currie coined the name "apoptosis" in 1972 [19]. Apoptosis is necessary for maintaining homeostasis and triggers a response to environmental changes. Its progression is influenced by factors such as aging, oxidoreductase status, neurotrophic factor support, mitochondrial dynamics, and stress. Apoptosis is controlled by a variety of inbuilt cellular processes, including pro- and antiapoptotic mechanisms that work in unison to ensure cell survival [20]. Apoptosis is primarily characterized by cell shrinkage, cell surface changes (blebs), nuclear reduction and shrinkage (pyknosis), and chromatin compression, which leads to the nucleus deforming and fragmenting into cellular waste. This process is accompanied by significant plasma membrane blebbing followed by karyorrhexis, membrane budding, chromatin aggregation, margination of condensed chromatin, DNA laddering (in agarose gel), and cell disintegration into apoptotic corpses. Apoptosis binding protein R, apoptotic protease activating factor-1 (Apaf1), apoptotic initiation factor (AIF), and tiny proteins released from mitochondria to the cytoplasm are the main participants in apoptosis (proteins of caspase family MAPK, BCL2, etc.) [21]. Apoptosis begins with the rounding of cells, which then shrink and lose touch with their surrounding cells. Following this, the cytoplasm undergoes changes that cause the endoplasmic reticulum to enlarge and the cisternae to inflate, forming vacuoles and vesicles. Chromatin condenses and aggregates into a compact mass during nuclear modifications, and endonucleases separate the mass into individual nucleosomes. The DNA ladder production process, which calls for the extraction of total or cytosolic cellular DNA and its separation in an agarose gel, allows us to see the entire progression. The apoptotic bodies include the fragmented nuclear masses. Disintegrated and complicated cell connections are present in the plasma membrane, and eventually blebbing is seen. The cell splits up violently, shedding the membrane spheres and packing the contents of the cell into apoptotic bodies of varying sizes. Apoptotic cells' plasma membranes naturally display recognition sites that allow phagocytic cells to recognize them. The apoptotic cells are almost completely segregated because of an unbroken plasma membrane, which

prevents cellular contents from leaking out and causing inflammation [19]. Contrary to necrosis, the entire apoptosis process operates in a coordinated manner and may therefore be interfered with, stopped, and modified. Necrosis is irreversible once it begins, does not involve localized events, and inflammation affects nearby cells once it has started, thus the therapies that can be used are difficult, limited, and complicated [22].

5.3 APOPTOSIS MECHANISM IN AD

The process of cell death known as apoptosis involves the activation of proteases, which obliterate cellular machinery. This pathway comprises a decreased potential of the mitochondrial membrane, intracellular acidification, production of free radicals, and externalization of phosphatidylserine residues [23, 24]. Apoptotic bodies are formed during this process, which minimizes immunological reactions and does not cause inflammation [25]. Cell death is carried out during apoptosis by activating caspases (serine proteases), which are prompted by a death signal delivered through receptor pathways. Both internal and external factors can initiate the process. These factors may differ, but they combine to create apoptotic bodies that are then ingested and consumed via efferocytosis [26]. Caspases are the main enzymes involved in apoptosis in mammalian cells, which is mostly carried out by intrinsic and extrinsic mechanisms. These are the enzymes that are predominantly in inactive forms (pro-caspases) and are activated by enzymes or apoptotic signals. The executioner caspases are subsequently triggered after the executioner caspases (mainly caspase 3). A key process that leads to the production of apoptosomes (Apaf-1 and caspase-9) is the release of cytochrome C from mitochondria. In short, the caspases 2, 6, and 10 break down the apoptotic cell through proteolysis when caspase-9 and caspase-3 are activated simultaneously. A death-inducing-signaling-complex (DISC) is formed when Fas, a member of the TNFα-superfamily undergoes Fas-ligand binding in the extrinsic pathway. Procaspase-8 is then cleaved and activated after the creation of the DISC, to further activate the downstream caspases such as caspase-3 to cause cell death [27]. Anti-apoptotic (Bcl2) and pro-apoptotic (Bax) proteins interact to cause the release of cytochrome C in the intrinsic pathway [28]. Effector caspases (3 and 7) are launched when initiator caspases (8 and 9) are activated. Caspase 9 is internally triggered by malnutrition, hypoxia, and cellular malfunction, which ultimately causes the release of cytochrome C from the mitochondria and the creation

of the apoptosome complex. Caspases 8 and cleaving Bid molecules can be shortened to generate anti-apoptotic molecules like Bcl-2, Bcl-xL, and Mcl-1. These proteins take involvement in the control and execution of cell death, and by controlling the release of cytochrome C, they can preserve or compromise mitochondrial integrity [29].

In neurodegenerative and inflammatory diseases, caspases are activated. The hippocampal degenerative granulovacuolar alterations are associated with caspase activation, which co-localizes with NFTs and is correlated with increased Aβ synthesis. When caspase-3 cleaves APP, it creates the neurotoxic peptide (C31), which causes cytotoxicity by inducing the production of Aβ and leaving Tau in the C-terminal region, along with the synthesis of NFTs [30].

A DNA repair enzyme called Ref-1 in the AD brain indicates DNA damage [31]. Synaptophysin, a protein related to synapses, is significantly decreased in the area around NFTs, indicating altered protein expression and synaptic loss prior to neuronal death in AD [32]. With increased expression of apoptotic molecules, the identification of activated caspases and cleaved substrates, significant endonuclease activity, and prostate apoptosis response protein-4 (Par4), there is ample evidence of apoptotic cell death in AD, suggesting that apoptosis is a key mediator of cell loss in the disease. Loss of anti-apoptotic molecule Bcl-XL functions and increased pro-apoptotic molecule (Bax/caspase3) activity are additional signs of dysregulated apoptotic pathway in AD [32, 33]. A good analogy between the loss of neurons in AD and the concurrent upregulation of pro-apoptotic proteins, particularly caspase 3, is made. Despite the fact that TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling) staining is associated with cell death, the results are riddled with errors because the TUNEL assay also finds DNA breaks that signify necrosis. In the AD brain, caspases 8 and 9 are overexpressed and encourage mitochondrial dysfunction. Caspase activation, which occurs before the production of NFTs in AD, is indicated by the circulation of tau fragments that have been broken by caspases [34].

5.4 APOPTOTIC PATHWAYS: APPROACHES FOR AD

Apoptosis is a crucial factor in cortical development as before the complete compilation of the neuronal population, over half of the neurons will perish. The two stages of apoptotic neuronal death are the first (embryonic) phase, which begins at day 14 and targets proliferating precursor cells, and the second (postnatal), which targets postmitotic neurons. In AD, a slight

modification of these phases may lead to neurodegeneration [35]. Caspase-3 and Bcl2 have an antagonistic interaction due to the anti-apoptotic function of Bcl2, which prevents caspase-3 and other pro-apoptotic proteins from being activated [36]. Numerous proteins are involved in the apoptosis mechanism, and creating a balance between pro- and anti-apoptotic factors is essential to maintain neuronal integrity [37]. The erratic state makes it difficult for neurons to survive and affects homeostasis. This equilibrium is consistent with the balance between pro-inflammatory and anti-inflammatory proteins (cytokines), kinases, phosphatases, oncogenes, and tumor suppressor genes.

To carry out apoptosis and control cell turnover, pro-apoptotic and anti-apoptotic proteins must coexist in equilibrium [20]. Based on the environment and the type of inducers, cells perceive, monitor, and determine whether to die or survive. The potential apoptotic signal causes cell death, but if it is premature or of insignificant intensity, the cell survives. A cooperative status of the pro- and anti-apoptotic machinery is necessary for this balanced condition [38–40]. The apoptotic program may still be active in AD at a significant but low level, but the lethal stages are postponed due to the presence of counteractive protective agents. Cells that lack anti-apoptotic genes become vulnerable to sublethal apoptotic stimuli, whereas cells with a high concentration of anti-apoptotic genes become defiant and resistant to apoptotic stimuli. The necessity of maintaining a balanced state of apoptotic and anti-apoptotic factors is demonstrated by the fact that the minimal stressor dosage needed to kill a cell overexpressing anti-apoptotic genes increases, while the opposite is also true [41]. Various apoptotic pathways have been shown in Figure 5.2.

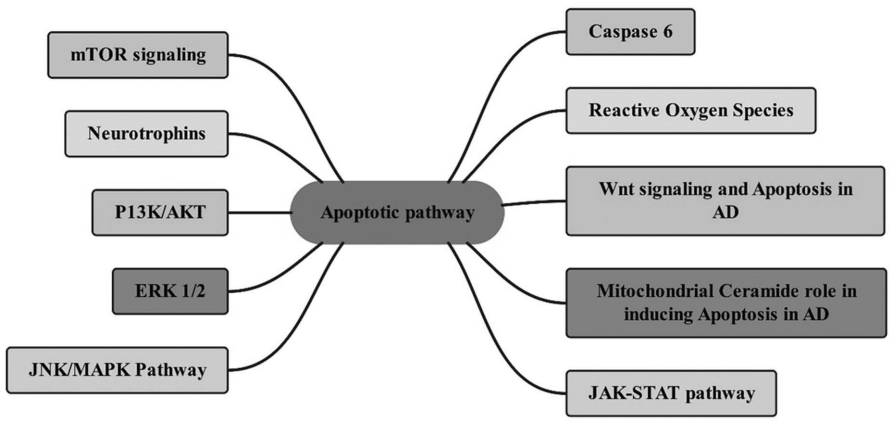

FIGURE 5.2 Apoptotic pathways for AD.

5.4.1 REACTIVE OXYGEN SPECIES (ROS)

The pathogenesis of AD is significantly influenced by oxidative stress, and the apoptotic program is dysregulated when the exacerbated situation is combined with a loss in antioxidant defense. Oxidative stress results in a rise in reactive oxygen species (ROS), increases blood-brain barrier permeability, changes cellular tubulin assembly, disrupts synaptic communication, and causes significant neuronal death in AD [42]. Normal ROS levels are necessary for many cellular and neuronal processes, including synaptic communication and neurotransmitter metabolism, but once they are increased, they become harmful for the development of AD. ROS result in apoptosis through mitochondrial and non-mitochondrial pathways. Although the ideal amounts of free radicals are necessary for regular apoptotic signaling and aid in the elimination of old and worn-out cells, the worsened condition causes failure of the membrane potential of mitochondria. Bax expression and the transfer of cytochrome C from the mitochondria to the cytosol are also prompted by a weakened antioxidant defense system in the hippocampus. Antioxidant therapy can stop this process by weakening the provoking apoptotic signals by overexpressing mitochondrial superoxide dismutase [43, 45]. Due to the fact that overexpression of mitochondrial superoxide dismutase protects against ischemia-induced injury, oxidative stress, which is the main regulator of oxidoreductase status of the cell, also causes neuronal death. It causes mitochondria to activate the anti-apoptotic ability of Bcl-2 to restrain the build-up of ROS and defend against lipid peroxidation of cell membranes [46].

5.4.2 CASPASE 6

Caspase 6 exhibits a high correlation with AD due to its co-localization with Aβ plaques and NFTs. Higher caspase-6 activity in the AD brain is associated with deficits in attention, worse episodic memory, inflammation, and neurodegenerative alterations [47]. Although this enzyme promotes axonal pruning, β-cell activation, plasma cell differentiation, and inappropriate activation through a series of upstream activators (Caspase 3 and 1) increases apoptotic cascade and may indicate the role of caspase-6 [48, 49]. In addition to upregulating caspase-6 transcription, the pro-apoptotic protein p53 also causes the production of neurotoxic peptide c-31 and other harmful substances. As a result, caspase-6 is a key upstream regulator of AD, and it may be helpful to inhibit caspase-6 while it is dormant to prevent the death of neurons due to apoptosis [50, 51].

5.4.3 JNK/MAPK PATHWAY

In AD brains, c-Jun N-terminal kinases (JNKs) are overexpressed and are involved in the formation of Aβ aggregates and NFTs. Extracellular signals must travel through the JNK pathway in order to reach the nucleus. JNK mediates cytokine suppression of protein synthesis and osmotic stress in the apoptotic signaling process. ROS, inflammatory mediators, and ischemia/reperfusion are a few of the variables that activate this system. In vertebrates, JNK is encoded by three different genes: JNK1, JNK2, and JNK3. While JNK3 is specifically expressed in the brain and is essential for initiating apoptosis, JNK1 and JNK2 are extensively expressed in the human system. The loss of neurons, protein malfunction, translational block, and gliosis caused by A may all be mediated by this system, which is particularly active surrounding Aβ [52–54]. JNK activation inhibits Bcl anti-apoptotic proteins and promotes toll-like receptor 4 (TLR4) signaling, which inhibits caspase 3 and has anti-apoptotic effects [55, 56]. TAT-TIJIP (Tat cell transporter sequence-bound truncated version of I-JIP), a JNK interacting protein, has also shown an anti-apoptotic effect through JNK inhibition, demonstrating the dual roles of JNK [57].

By directly phosphorylating apoptosis-related proteins like BIM (homologous to Bax) and BMF, which changes membrane potential and starts the release of cytochrome C from mitochondria, JNK exhibits an apoptotic role. Anti-apoptotic proteins DP5-HRK, Bcl-2, and Bcl-xL are also phosphorylated by JNK [58]. Overall, JNK promotes c-JUN, which results in altered transcription of genes that promote apoptosis and neuronal death [59].

5.4.4 ERK1/2

Through its interaction with TNF-α, Fas ligand, osmotic pressure, ischemia, trophic factor withdrawal, nitric oxide, hydrogen peroxide, and chemotherapy stimuli, ERK1/2 activation prevents apoptosis. After being stimulated by these inducers, ERK1/2 is briefly activated, exerting an anti-apoptotic effect. Although the ERK1/2 pathway inhibits caspase 8 activity and Bid cleavage, it has no effect on the mitochondrial transmembrane potential or the release of cytochrome C. Additionally, the pathway deactivates the pro-apoptotic Bcl-2 relative BAD, which is phosphorylated by ERK and PI3K/AKT signaling and activated. By phosphorylating Ser136 in p70S6 kinase, ERK downstream regulates BAD function, and nerve growth factor (NGF) also

inhibits apoptotic Bcl-2 via the MEK-ERK1/2 pathway. Furthermore, NGF phosphorylates Bim at Ser109 and Thr110 via the MEK-ERK1/2 pathway, weakening its anti-apoptotic function. Additionally, ERK1/2 enhances anti-apoptotic signaling and promotes cell survival through a variety of mechanisms. IEX-1 (NFκB target) and Mcl-1 (an anti-apoptotic factor) are also phosphorylated by ERK1/2 at Thr18, which inhibits cytochrome c-mediated mitochondrial signaling [60]. Protein synthesis inhibitors and antioxidants reduce ERK activation, whereas MEK1Q56P overexpression increases ERK and initiates apoptosis [60–62].

5.4.5 PI3K/AKT

The phosphoinositide-3 kinase (PI3K)/AKT pathway is one of the key apoptotic counteractive pathways that is still active in neurodegenerative diseases. By triggering the PI3K pathway, the AKT (v-AKT murine thymoma viral oncogene)/PKB (protein kinase-B) mediates neuronal cell survival. Phosphatidylinositol-3,4,5-trisphosphate, which is produced by the active PI3K and aids in attracting AKT to the membrane, is a membrane phospholipid. Through heterodimerization, phosphorylated AKT activates prosurvival mechanisms, such as the Bcl-2 family, and represses the mitochondrial death pathways [29].

There are three isoforms of the serine-threonine kinase AKT: Akt1, Akt2, and Akt3. However, Akt2 is distributed across the somatic layers of the hippocampus and astrocytes, suggesting that it may have a dominant function to play in the cognitive domain [63].

FKHs (forkhead) proteins govern the expression of genes that control the cell cycle and cell death, such as Fas L, which is overexpressed in AD and mediates apoptosis caused by Aβ. Additionally, the PI3K/Akt pathway suppresses JNK signaling while activating NF-κB. The inhibitory subunit IkB, which confines the NF-κB complex in the cytoplasm, is phosphorylated to release NF-κB, which then translocates to the nucleus and activates the transcription of genes that support resistance to apoptosis, including Bcl-2 and members of the family of Inhibitors of Apoptosis Proteins (IAPs) [64].

The PI3K/AKT/mTOR pathway was overactivated in AD, and kinases such as PI3K and ERK2 were induced to phosphorylate AKT and mTOR in the AD brain [65]. PTEN (*Phosphatase and tensin homolog)* inhibits PI3K/AKT signaling, and a decrease in PTEN causes an increase in Akt signaling. Anti-apoptotic signals may be overwhelmed in this hyperactive state and propagate unfortunate pathways. In the AD hippocampus and temporal

cortex, there has been a significant loss of PTEN-positive neurons, and PTEN correlates negatively with the severity of NTFs and with Aβ levels [66, 67]. In cortical neurons, disruption of Akt2 and Akt3 results in a modest but significant loss in cell viability, which is correlated with the activation of caspase 3 [68]. Therefore, persistent activation of this pathway changes the pro-survival and anti-apoptotic function of PI3K/AKT.

5.4.6 NEUROTROPHINS

The growth and development of all differentiated cells, including neurons, depends on trophic substances to prevent apoptosis and premature cell death. Neurotrophins, such as NGF, BDNF, neurotrophins 3, 4, and 5 (NT3, NT4/5, and NT6), inhibit the death of neurons. These elements link with the high-affinity receptors Trk A, B, and C and disengage some specific apoptotic pathways. Neurotrophins not only preserve trophic-deficient neurons but also increase the resilience of nerve cells by ensuring defense against excito-toxicity, ischemia, and many neurodegenerative hazards [69]. The ability of Neurotrophins to inhibit apoptosis is mediated by their interaction with the activating kinases Erk1/2 [77] and PI-3 K via Trks [70].

Erk1/2 and PI3K ensure the longevity of neurons, prevent premature death, and aid in avoiding harmful stimuli [71]. The apoptotic pathway, which is essential for the protective effects of NGF, EGF, insulin, and serum on PC12 cells, is fiercely opposed by PI3K [72].

5.4.7 MTOR SIGNALING

By controlling pro-apoptotic proteins, mTOR signaling disruption may result in neuronal degeneration and aberrant neural development [73]. Apoptotic proteins are expressed more frequently and anti-apoptotic proteins are expressed less frequently in AD, which results in the build-up of Aβ, NFTs, and neuronal death [74–76]. The MAPK/ERK1/2 and p90 ribosomal S6 kinase-induced apoptosis are both activated by phosphorylated mTORC1 [77–79].

5.4.8 JAK-STAT PATHWAY

The JAK-STAT pathway has a significant role in the control of apoptosis and inflammasome activity in AD. By activating microglial cells, the amyloid build-up speeds up the neuroinflammation processes and damages neurons by overactivating the JAK-STAT pathway. The cytokines bind to their type II

receptor and activate JAK, which then phosphorylates STAT 1 and STAT 3. STAT 1 and STAT 3 then translocate to the nucleus and bind to the interferon (IFN) target gene promoters and regulate apoptosis by releasing cytochrome C into the cytosol, which in turn activates caspase 3 and causes neuronal apoptosis in AD [80]. Thus, cytochrome C discharge and caspase initiation are brought about by the momentary stimulation of STAT1 and STAT3. IFN essentially activates STAT1 to trigger apoptosis by upregulating p21 and activating caspase-3.9 [81].

5.4.9 MITOCHONDRIAL CERAMIDE ROLE IN INDUCING APOPTOSIS IN AD

In the lipid cell membrane of neurons, cholesterol contributes to the production of Aβ clusters and increases their stickiness. Other lipids, like ceramides and related sphingolipids, are also becoming more and more important in the development of Aβ cluster-induced neuronal death [82–85].

Ceramides then promote the production of ROS leading to oxidative stress resulting in apoptotic signaling, activating defense mechanisms, and the migration of microglial cells, which release neurotoxic molecules (i.e., TNF-α, IL-1, and IL-6) [86]. Ceramide, a bioactive sphingolipid, functions as a signaling molecule that controls metabolism, pro-apoptotic signaling, and stress responses in neurodegeneration [87]. Ceramide levels are elevated in the cerebrospinal fluid (CSF) of AD patients, and these elevated levels point to the potential role of ceramide in the pathogenesis of the disease through the production of APP and activation of mitochondrial disturbance, which leads to mitochondrial membrane permeability and neuronal death [86, 88]. This further boosts the generation of ROS, releasing cytochrome C and activating caspase 3, which then mediates the apoptotic death of neurons. Ceramides contribute to neuronal apoptosis by modulating the expression of the apoptotic proteins Bax and BAD as well as the various signaling cascades of PI3K/AKT, mitogen-activated protein kinases (MAPKs), and other signaling pathways [87, 88].

5.4.10 WNT SIGNALING AND APOPTOSIS IN AD

In Alzheimer's disease (AD), the build-up of Aβ is a factor in the decrease of synaptic plasticity or problems with the integration of memory formation (Long-term potentiation). By controlling NMDA receptor-dependent

LTP, which boosts synaptic strength and controls synaptic transmission and architecture, Wnt signaling significantly contributes to maintaining synaptic plasticity. Wnt proteins interact with the frizzled family of receptors to alter neurotransmission both pre- and post-synaptically. Numerous studies have linked dysregulation of Wnt signaling to modifications in synaptic transmission and altered hippocampal neurons [89, 90]. The Wnt function of modulating neurotransmission appears to be disrupted in AD, as evidenced by decreased Wnt protein levels and altered Disheveled-1 (Dvl1) scaffolded protein [90]. Through various receptors, Wnt proteins like Wnt 7a, Wnt 5a, and Wnt 3a modify pre-synaptic neurotransmission by either generating frizzled-5 and creating pre-synaptic sites or by expanding pre-synaptic sites and controlling vesicle recycling [90, 91]. Wnt signaling also controls the development of post-synaptic excitatory synapses by boosting calcium flux through NMDA and AMPA receptors, which activates CaMKII's downstream signaling and encourages exocytosis [91]. So, restoring Wnt signaling may be a tactic to prevent neuronal degeneration, which will also work in concert with its antioxidant and anti-excitotoxic potential.

5.5 ANTI-APOPTOTIC ROLE OF NATURAL MOLECULES IN ALZHEIMER'S DISEASE

5.5.1 GELSOLIN

The cytoplasmic architecture of the cell is preserved by tightly regulated actin filament assembly regulation. A significant actin-binding protein called gelsolin caps the developing end of the actin filament, promotes its nucleation, and severs the actin filaments [92]. One molecule of gelsolin and two molecules of actin form a calcium-dependent bond. Ca^{2+} and phosphoinositide's control the intracellular activities of gelsolin [93]. Gelsolin is present intracellularly and as a secreted protein in the plasma and CSF [94]. The disulfide structure differs between intracellular gelsolin and plasma/CSF, which both result from alternative splicing of a single 70 kbp long gene (including at least 14 exons). Five cysteine (Cys) residues may be found in gelsolin at positions 93, 188, 201, 304, and 645. Human cytoplasmic gelsolin contains five Cys residues, all of which are free thiols. In contrast, plasma/CSF gelsolin contains four Cys residues, three of which are free thiols at positions 93, 304, and 645, and two of which are disulfide-linked [95] (Figure 5.3).

Additionally, plasma/CSF gelsolin varies from the cytoplasmic version at the amino-terminus by an additional 25 amino acid residues [95]. About 179 μg/ml is the physiological concentration of gelsolin in plasma, which is substantially higher than the concentrations of apo E (54±20 μg/ml) and apo J (35–105 μg/ml). According to Paunio et al., gelsolin diffuses from serum to CSF based on the association between the ratios of the gelsolin content in serum and CSF [96]. Other researchers have hypothesized that gelsolin in CSF may come from microglia [97] or oligodendrocytes [98]. Several investigations have suggested that gelsolin is involved in processes other than the regulation of actin polymerization, including the modulation of calcium channels and N-methyl D-aspartate (NMDA) receptors, apoptosis, and tumor suppression [99, 100]. It should be noted that gelsolin is amyloidogenic due to an Asp187Asn or Asp187Tyr mutation and thereby a rare hereditary amyloid polyneuropathy known as gelsolin-related amyloidosis can develop. Due to the mutations between the residues 172 and 173, gelsolin is cleaved abnormally within the cell, producing the amyloidogenic 173–243 fragment [101].

5.5.1.1 BINDING OF GELSOLIN TO Aβ

The binding of gelsolin to Aβ was verified by fixing the Aβ to a nitrocellulose membrane in the gelsolin overlay assay [102]. According to the findings, the amounts of both gelsolin and Aβ are necessary for the binding of Aβ to gelsolin [102]. Microplate-based solid-phase binding assays revealed that there are two Aβ-binding sites on gelsolin with Kds of 1.38 μM and 2.55 μM, and that the binding of Aβ with gelsolin is saturable. The dissociation constant of the Aβ-gelsolin complex is within the range of the physiological concentration of gelsolin because the levels of gelsolin in the plasma are in the micromolar range, or 2 μM [96].

5.5.1.2 ANTI-APOPTOTIC ROLE OF GELSOLIN

Alzheimer's disease (AD) is characterized by neuronal cell loss. According to a number of studies, Aβ causes more oxidative stress, which leads to the death of neuronal cells [103, 104]. Gelsolin was found to reduce Aβ-induced neurotoxicity in a study [105]. Additionally, it was noted that PC-12 cells undergo apoptosis when H_2O_2 produces oxidative stress [106]. According

to a recent study, H_2O_2 treatment of PC-12 cells results in an increase in cytoplasmic gelsolin expression [107].

5.5.2 CAROTENOIDS

A family of yellow, orange, and red pigments called carotenoids is present in algae, fungus, bacteria, and plants. By widening the spectrum of light wavelengths that power the process, carotenoids contribute significantly to photosynthesis. Additionally, carotenoids shield photosynthetic organisms from harm brought on by excessive light exposure [108, 109]. In nature, there are more than 600 different kinds of carotenoids. According to their chemical makeup, carotenoids can be divided into six main groups: hydrocarbons, hydroxy carotenoids, epoxy carotenoids, aldehydes, ketones, and carboxylic acids [110]. Based on the chemical components of the many forms of carotenoids, carotenes, and xanthophylls are divided into two major classes. According to their structure, which solely contains a parent hydrocarbon chain, carotenes are classified as lycopene, β-carotene, and β-carotene [111]. The structures known as beta-cryptoxanthin, neoxanthin, astaxanthin, canthaxanthin, zeaxanthin, fucoxanthin, and lutein are examples of xanthophylls that have oxygen as a functional group [111].

The human diet contains a lot of carotenoids, with foods like fruits and vegetables having rich color (pigmentation). Additionally, it has been shown that the blood and tissues of the human body contain nearly 20 different forms of carotenoids [112].

5.5.2.1 LYCOPENE

The reddish-pink hue of some fruits and vegetables, such as tomatoes, grapefruit, watermelon, and guava, is due to the pigment lycopene. Chemically, it is an eight-isoprene unit assembly of a hydrocarbon carotenoid, which only contains carbon and hydrogen. Lycopene is primarily found as trans-lycopene in fresh fruits and vegetables. Trans-lycopene undergoes isomerization to cis-lycopene when exposed to heat [113]. Numerous clinical research has shown that cis-versus trans-lycopene has a higher absorption and bioavailability [114–116]. Lycopene has been extensively studied, and there may be advantages in terms of cancer, cardiovascular illness, and inflammatory disease [117] (Figure 5.3).

The levels of lycopene in the liver, adrenals, spleen, lymph nodes, and intestinal tissues of dogs were increased by oral administration of lycopene, but lycopene in the brain was not found [118]. However, oral lycopene administration (8 mg/kg) raised the lycopene content in mouse brain, and a lycopene-loaded microemulsion was used to optimize this delivery strategy, dramatically improving lycopene dispersion in the brain [119]. Lycopene application has been demonstrated to shield brain cells from oxidative stress-related harm. *In vitro* and *in vivo* models of neurodegeneration treated with lycopene prevent the accumulation of hydrogen peroxide and superoxide as well as the lipid peroxidation of membranes [120–124]. By oxidant and cell type, the antioxidant effectiveness of lycopene may vary. Superoxide dismutase, catalase, glutathione peroxidase, and glutathione are just a few of the intracellular antioxidant defense system components that are upregulated by lycopene [122, 124, 125]. The antioxidant capabilities of lycopene are crucial for preserving mitochondria [120, 121, 125].

Additionally, mitochondria are in charge of producing ROS [126]. Excessive ROS build-up and compromised antioxidant defenses cause mitochondrial malfunction, which leads to energy depletion, apoptosis initiation, and ultimately neuronal death in the brain [127, 128]. When exposed to ROS, lycopene therapy reduces the loss of mitochondrial inner membrane potential [121, 125, 129].

Under neurotoxic conditions, lycopene inhibits pro-apoptotic proteins like Bax while preventing the loss of anti-apoptotic proteins like Bcl-2 and Bcl-xL [123, 130]. By preventing the opening of mtPTP, lycopene shields primary hippocampal neurons from apoptotic death [131]. Lycopene-treated neurons exhibit preserved mitochondrial membrane integrity as evidenced by a decrease in mitochondrial depolarization and cytochrome C release [125, 131].

Lycopene therapy enhances Akt phosphorylation [121, 122]. When phosphoinositide 3-kinase (PI3K) is activated, AKT, also known as protein kinase B, is phosphorylated. Phosphorylated AKT controls transcription factors including nuclear factor erythroid 2-related factor 2 (Nrf2) and NF-κB, which affects gene expression. Indeed, lycopene has been demonstrated to influence Nrf2 and NF-κB targets, reducing damage to brain cells caused by oxidative stress or inflammation [123, 132]. Pro-inflammatory prostaglandins are primarily produced by the cyclooxygenase-2 (COX-2) pathway, which is mediated by lycopene [133, 134]. Lycopene also inhibits the release of inflammatory cytokines and chemokines like interleukin (IL)-6 and IL-8 as well as acute phase proteins like C-reactive protein (CRP) [135, 136].

By reducing the build-up of inflammatory cytokines in the brain, lycopene treatment improves stress-related behavior in mice [137, 138]. Neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) are produced more effectively when lycopene is administered intracerebroventricularly *in vitro* and *in vivo* [121, 139]. Lycopene's antioxidant qualities are particularly crucial for safeguarding mitochondria [120, 123, 125]. Because they contain the electron transport chain, mitochondria are the primary oxygen-consuming organelles, but they are also the source of reactive oxygen species (ROS) [126]. Excessive ROS buildup and compromised antioxidant defenses cause mitochondrial malfunction, which leads to energy exhaustion, the start of apoptosis, and ultimately neuronal death in the brain [127, 128]. When exposed to ROS, lycopene therapy reduces the loss of mitochondrial inner membrane potential [121, 125, 129]. Under neurotoxic conditions, lycopene inhibits pro-apoptotic proteins like Bax while preventing the loss of anti-apoptotic proteins like Bcl-2 and Bcl-xL [123, 130]. By preventing the opening of mtPTP [121, 123], lycopene shields primary hippocampal neurons from apoptotic death [131]. Lycopene treatment reduced mitochondrial depolarization and cytochrome c release in neurons, indicating that mitochondrial membrane integrity was maintained [120, 125].

5.5.2.2 B-CAROTENE

The red and orange hues found in some fruits and vegetables, including carrots, sweet potatoes, and squash, are caused by the carotenoid *β*-carotene. It has *β*-rings at both ends of an unsaturated hydrocarbon chain. Two molecules are released when *β*-carotene is symmetrically cleaved by *β*-carotene-15,15-oxygenase, an aldehyde type of vitamin A called retinal [140–142]. Retinal is subsequently processed to produce vitamin A compounds such as retinoic acid, retinol, and retinyl ester, respectively [140, 141]. Consequently, *β*-carotene is a crucial provitamin A. Hydrogen peroxide and lipid peroxide radical build-up are reduced by *β*-carotene [143, 144]. Due to its scavenger function, *β*-carotene is classified as a direct-acting low molecular weight antioxidant. *β*-carotene has a significant role in illnesses associated with the brain because it can reduce oxidative stress and fight lipid peroxidation [145]. Traumatic brain damage is a consequence of a lower level of *β*-carotene in the cerebral cortex [146]. Since *β*-carotene does not exhibit pro-oxidant activity in the brain, it has been proposed as a safer antioxidant

in contrast to vitamin A, which can cause oxidative stress with excessive therapy [143] (Figure 5.3).

NAD(P)H quinone dehydrogenase and heme oxygenase-1 are two downstream targets that are upregulated by β-carotene and include antioxidant response elements (ARE) [147]. Since oxidative stress plays a significant role in the death of neurons during neurotoxicity, therapy with β-carotene may stop the loss of neurons in conditions involving ROS in the brain. In a mouse model of traumatic brain damage, treatment with β-carotene inhibits the loss of Bcl-2 and the build-up of Bax and caspase 3 [147]. The cognitive and social behavior is improved by β-carotene in newborn mice [148].

5.5.2.3 ASTAXANTHIN

Algae, yeast, salmon, trout, krill, shrimp, and crayfish are all naturally rich sources of red-orange carotenoid known as astaxanthin [149]. Carbon, hydrogen, and oxygen make up this xanthophyll carotenoid. Chemically, it is made up of two terminal rings that are connected by a polyene chain and have a hydroxyl and a carbonyl group on each [150]. Astaxanthin has significant antioxidant properties because the polyene chain contains conjugated double bonds, which lead to delocalization of electrons that can be easily transferred [151]. According to studies, astaxanthin has anti-lipid-peroxidation [152], anti-inflammatory [153], anti-diabetic [154], and anti-cancer activities [155], as well as the ability to prevent cardiovascular disease [156] and to modulate the immune system [157]. Although astaxanthin has a low oral bioavailability, eating it along with lipids improves absorption [158]. All-trans-astaxanthin is found in the rat cortex and hippocampus after oral treatment of astaxanthin (100 mg/kg), demonstrating that it can penetrate the blood-brain barrier due to its lipophilic nature [159]. It has been demonstrated that astaxanthin has antioxidative protective effects in neurological disorders. It lowers lipid peroxidation markers such as malondialdehyde, reduces ROS-generating enzyme protein levels such as NADPH oxidase 4 and p22phox protein, and increases antioxidant enzyme superoxide dismutase [160]. Additionally, it has been shown that astaxanthin increases the protein levels of Nrf2 and p62, providing defense against oxidative stress [160, 161]. By regulating mitochondrial proteins, astaxanthin also protects against apoptosis [160–163]. In rat hippocampal neurons, astaxanthin treatment inhibits the loss of mitochondrial membrane potential [162] (Figure 5.3).

Moreover, astaxanthin appears to have anti-inflammatory actions with protective effects [160, 161]. The NF-κB pathway controls the synthesis of cytokines and chemokines and is a pro-inflammatory mechanism [164]. NF-κB binds to the inhibitor of nuclear factor kappa-κB (IκBα) and remains in the cytoplasm while inactive. However, when NF-κB is activated, IκBα is separated from it, and NF-κB is translocated into the nucleus to regulate gene expression. In the brain and hippocampus of patients receiving astaxanthin therapy, total and nuclear NF-κB protein levels are reduced [160, 163]. By decreasing neuroinflammation and modulating survival pathways including PI3K/AKT, astaxanthin administration also reduces depressive-like behaviors in rodents [165–167].

By inhibiting the Na^+–K^+-$2Cl^-$ co-transporter-1 (NKCC1), a crucial transporter linked to brain edema, via the NF-κB pathway, astaxanthin reduces swelling of brain cells. It has been demonstrated that NKCC1 inhibition reduces blood-brain barrier disruption and has a neuroprotective effect [168].

5.5.2.4 LUTEIN

Lutein is a carotenoid that originates from plants and is present in meals like eggs and avocados as well as green leafy vegetables like spinach, kale, and broccoli. Being isomeric with zeaxanthin, lutein has an unsaturated hydrocarbon chain with cyclic structures at each end. It is the only carotenoid to pass the blood-retina barrier and be discovered in the macula of the eye, along with zeaxanthin [169]. Treatment with lutein reduces retinopathy brought on by oxidative, inflammatory, and photostress [170–172], and dietary lutein shields the eyes from age- and diabetes-related illnesses [173, 174]. Additionally, lutein can get across the blood-brain barrier and reach different parts of the brain. After oral treatment with lutein at 0.25–0.5 mol/kg, the cortex of rhesus monkey, cerebellum, striatum, and hippocampus were found to contain lutein [175, 176]. Therefore, research on the advantages of lutein for brain growth and potential anti-degenerative actions is increasingly becoming significant [177, 178].

During an ischemic challenge, lutein replenishes other antioxidants such as glutathione, superoxide dismutase, and catalase in the brain [179]. Intriguingly, Mohn et al. demonstrated that fatty acid oxidation in the primate brain is inversely correlated with lutein levels in the mitochondrial membrane [176]. In *Caenorhabditis elegans* lacking nuo-5/NDUFS1 and lpd-5/NDUFS4 genes, lutein treatment greatly reduces mitochondrial ROS.

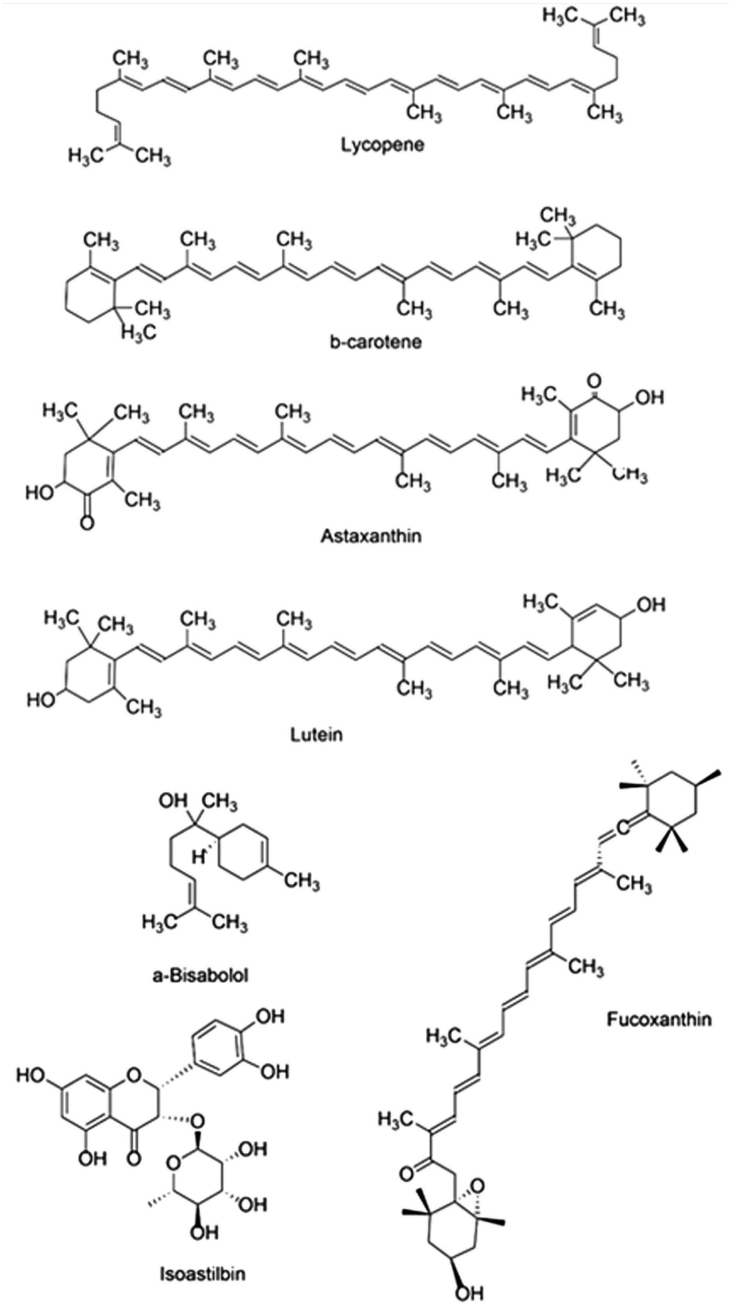

FIGURE 5.3 Structures of potential natural anti-apoptotic compounds for the management of AD.

Lutein may influence the transcription of genes that govern inflammation and antioxidant activity because it boosts Nrf2 and reduces NF-κB component p65 [180–184]. Lutein treatment prevents apoptosis in neurons and cells generated from the brain. In brain disease models of cerebral ischemia and Parkinson's disease, lutein inhibits the loss of Bcl-2 and Bcl-xL, accumulation of Bax, and activation of caspases 3 and 8 [184–186]. A key protease called caspase 3 is in charge of carrying out apoptosis and destroying the cellular framework.

Lutein may successfully counteract the apoptosis that is brought on by glutamate-mediated excitotoxicity. Excess glutamate stimulates NMDA receptors during cerebral ischemia and neurodegeneration, causing a spike in intracellular calcium. Calpain and phospholipases are two damaging enzymes that are activated by this surge and result in the death of neurons. Lutein inhibits death signals, such as MAPK-mediated c-Jun activation, and reduces loss of retinal ganglion cells in response to NMDA stimulation [184, 186].

5.5.2.5 FUCOXANTHIN

Brown seaweed contains a carotenoid called fucoxanthin that has anti-inflammatory and antioxidant effects. The ability of fucoxanthin to pass the blood-brain barrier is unknown. Middle cerebral artery occlusion (MCAO) causes neurological deficits and brain tissue destruction in mice, although fucoxanthin therapy can restore this MCAO-induced brain damage [187]. In animals suffering from neurodegeneration and ischemic insults, fucoxanthin treatment enhances cognitive and motor function [187–189]. Fucoxanthin can be administered intragastrically and intracerebroventricularly to treat ischemic stroke and traumatic brain injury in mice by increasing Bcl-2 levels and lowering Bax, cytochrome C release, and caspase 3 activity [187, 190]. Strong radical scavenging action is present in fucoxanthin and its metabolites [191]. Fucoxanthin, for instance, has 13.5 times more hydroxyl radical scavenging activity than α-tocopherol [191].

Fucoxanthin may directly occupy the docking site in addition to scavenging ROS, changing how proteins function. Fucoxanthin may directly bind to amyloid-β, inhibiting the development of pathogenic amyloid fibrils [192]. Fucoxanthin controls genes that are sensitive to antioxidants to control intracellular redox state. It also protects the mouse brain against neurotoxic insult by activating the transcription factor Nrf2 and its redox-sensitive

targets, including heme oxygenase-1, superoxide dismutase, and Bcl-2 expression, according to studies. In animals missing Nrf2, fucoxanthin is unable to reverse apoptosis, demonstrating the need for Nrf2 for fucoxanthin-mediated neuroprotection [187–190]. During neurotoxic stimulation, fucoxanthin demonstrates protective qualities by activating the PI3K/AKT pathway [193, 194].

Carotenoids block the upstream triggers of apoptosis and ROS-associated mitochondrial dysfunction due to their antioxidant potential, thereby preventing the energy deficit and subsequent activation of mitochondria-derived apoptotic molecules. In addition, they also affect various transcription factors such as Nrf2 and NF-κB to regulate apoptotic genes, antioxidant defense, and inflammation [195].

5.5.2.6 A-BISABOLOL

α-bisabolol is a naturally occurring sesquiterpene alcohol which is mainly present in plants such as *Matricaria chamomilla*. It possesses various therapeutic activities such as antioxidant, anti-inflammatory, anti-angiogenic, and antibiotic and is also used as food ingredient in pharmaceuticals [196]. The bioavailability and biocompatibility of α-bisabolol are very low due to its lipophilic nature, which minimizes its use for human disorders. Literature reports have demonstrated that the encapsulation of nanoparticles of α-bisabolol enhances its bioavailability and biocompatibility. For instance, α-bisabolol-loaded citric acid cross-linked zein nanofibrous scaffolds possess wound repair potential in *in-vivo* studies [197]. Moreover, α-bisabolol loaded in poly(lactic-co-glycolic acid) nanoparticles showed significant anti-inflammatory activity by decreasing the release of pro-inflammatory markers such as IL-12, IL-23, IL-6, and TNFα [198].

Solid lipid nanoparticle (SLNs)-based drug delivery system is receiving great attention in modern pharmaceutical research, especially in drug delivery and as clinical medication for the treatment of various disorders [199]. SLNs act as a novel colloidal carrier in pharmaceuticals as they possess unique properties such as small particle size, increased drug stability, biocompatibility, increased protection of drugs against enzymatic metabolism, and high drug loading capacity with a huge surface area [200]. SLNs are a promising candidate for the delivery of drugs to the central nervous system due to their natural tendency to cross the BBB [199].

Previous studies have reported the enhanced bioavailability and biocompatibility of α-bisabolol loaded SLNs (ABS) [201]. In addition, the antioxidant and anti-cholinesterase activities, the ability to inhibit fibrillization of Aβ peptide, and the ability to destabilize the preformed Aβ mature fibrils were also increased in the ABS as compared to the α-bisabolol alone. Furthermore, the role of ABS was also assessed for its neuroprotective potential against AD. It was demonstrated that ABS inhibits the macromolecular damage and oxidative stress by efficiently scavenging ROS/RNS in Neuro-2a cells *in vitro*. It also inhibited the β-secretase enzyme and apoptosis-mediated cell death in Neuro-2a cells induced by Aβ, suggesting its significant neuroprotective potential by targeting various neurotoxic mechanisms that are involved in the progression of AD [202].

5.5.2.7 ISOASTILBIN

Isoastilbin (IAB), is a dihydroflavonol glycoside compound and widely distributed in in various plants such as *Rhizoma Smilacis glabrae* and *Astragalus membranaceus*. It was reported that IAB possesses significant antioxidant potential and astilbin, an isomer of IAB demonstrated improved cognitive abilities in transgenic mice with AD by regulating the protein kinase-B/glycogen synthase kinase-3β signaling pathway [203, 204].

Mitochondria play a significant role in the pathogenesis of neurodegenerative disorders as a primary cellular source of ROS [205]. The overproduction of ROS and other cytokines, including cytochrome c, which triggers the cell apoptotic program, is a further consequence of the breakdown of mitochondrial homeostasis brought on by high levels of ROS [206, 207]. However, as oxidative stress develops, the transcription factor NF-E2p45-related factor 2 (Nrf2) aids in maintaining cellular redox homeostasis and supports the structural and functional integrity of the mitochondria [208]. Neurons are harmed by the extremely high levels of glutamate (Glu), a central nervous system neurotransmitter, associated with ROS accumulation. Additionally, in mice with AD, the loss of Nrf2 can result in higher intracellular levels of A [209].

5.5.2.7.1 Cell Apoptosis Assay

PC12 cells were plated into 6-well dishes at a density of 5 x 10^5 cells/well, pre-treated for 3 hours at 37°C with 10 or 30 μM of IAB, and then

co-incubated for 24 hours at 37°C with 25 mM L-Glu. Using a Muse™ Cell Analyzer flow cytometer (EMD Millipore, Billerica, MA, USA) and propidium iodide/Annexin V staining, the rate of cell apoptosis was calculated using the early and late stages of apoptosis. The data was then analyzed using Muse 1.4 Analysis (2010).

The protective effect of IAB in AD was investigated using L-glutamic acid-induced apoptosis of PC12 cells and $AlCl_3$ combined with D-galactose (D-gal)-developed Alzheimer's disease in mice. Pre-incubation of PC12 cells induced by L-Glu with IAB for 3 hours prior to treatment with 25 mM L-Glu decreased cell viability, inhibited apoptosis, suppressed the accumulation of intracellular reactive oxygen species, and restored mitochondrial membrane potential. Moreover, IAB treatment for 28 days also decreased the escape latency time in the water maze test, suppressed chronic movement in the open field test, and enhanced the ability to seek hidden food in a Y maze test, suggesting improved abnormal behaviors. In addition, the deposition of Aβ and phosphorylated-Tau expression in mouse brains were reduced by IAB, and it also enhanced the levels of serum Aβ. Furthermore, IAB regulated the expression of pro- and anti-apoptotic proteins in cells and brain tissue, and enhanced the nuclear levels of NF-E2p45-related factor 2 (Nrf2), expression of superoxide dismutase 1, catalase, and heme oxygenase-1 and -2, suggesting the potential role of IAB against AD pertaining to its antioxidation and anti-apoptotic properties (2011).

5.6 CONCLUSION

Apoptosis is a versatile and tightly regulated biological process which keeps the cell numbers in check and is also vital for various biological processes. However, the importance of apoptosis is unquestionable; nonetheless, the apoptotic programs are required to work in a well-balanced manner. The pathological indications of apoptosis are evident in various neurodegenerative diseases such as AD. In the case of AD treatment, targeting apoptosis in a controlled manner results in neuronal survival according to the state, stage, and type of inducers. Therefore, understanding the molecular pathways associated with apoptotic neuronal death modulation of several apoptotic signaling by targeting apoptotic factors may be a preventive strategy in AD. This chapter sheds some light on the role of various anti-apoptotic molecules from natural sources for their use in the treatment of AD through various anti-apoptotic pathways. These natural molecules have been reported to

possess significant anti-apoptotic potential in various models of AD via various pathways. However, more preclinical studies are required to explore the exact anti-apoptotic mechanism of the aforementioned molecules in AD. In addition, the reported molecules in this chapter can be further used by health practitioners to evaluate their effectiveness in AD patients.

KEYWORDS

- **Alzheimer's disease**
- **anti-apoptotic potential**
- **anti-apoptotic properties**
- **antioxidation**
- **apoptosis**
- **apoptotic factors**
- **dementia**
- **herbal drugs**

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CHAPTER 6

Potential Natural Polysaccharides for the Management of Alzheimer's Disease

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ABSTRACT

Neurological disorders are a class of diseases that affect the spine, brain, and the nerves connecting them, leading to an imbalance between neurotransmitters like dopamine and serotonin, and the loss of neurons resulting in impaired activities. Among these neurological disorders, Alzheimer's and Parkinson's are the most common neurological disorders as reported by WHO. Diet and nutrition are the most important health paradigms due to the increased sedentary lifestyle disorders. Instead of managing and treating diseases, preventive healthcare is the new outlook. Nutraceuticals are becoming prominent as they reduce the exorbitant use of synthetic drugs and also combat the disease by providing nutritional value. Polysaccharides have significant neuroprotective and reparative properties, which is now a breakthrough for the treatment of neurodegenerative disorders. As these plant-derived bioactive compounds (polysaccharides) are prone to degradation and chemical instability, they are encapsulated in nanostructured drug delivery systems. This chapter discusses seaweed polysaccharides, microbial polysaccharides, and their nanostructures as nutraceuticals in the treatment of neurodegenerative disorders.

6.1 INTRODUCTION

Neurodegenerative disorders result from a progressive loss of cognition and physical function. Alzheimer's, Parkinson's, and Huntington's disease are

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the most common neurodegenerative disorders. These neurodegenerative disorders either cause movement abnormalities or dementia. Alzheimer's is the most common dementia-causing neurodegenerative disorder. Due to an increase in the concentration of misfolded and insoluble tau protein, Alzheimer's disease is called tauopathy. Tau is normally not harmful to the body and is also soluble in nature but during Alzheimer's disease tau protein gets misfolded and hyperphosphorylated resulting in an insoluble harmful mass to the body [1]. Similarly, amyloid-β_{42} misfolded protein becomes toxic in nature. Misfolded tau protein and amyloid-β_{42} are the potential targets for the treatment of Alzheimer's Disease.

Seaweeds are major sources of energy that are categorized based on their pigmentation: brown seaweed (*Phaeophyta*), green seaweed (*Chlorophyta*), and red seaweed (*Rhodophyta*). Seaweed mostly relies on sulfated polysaccharides to build its flexible cell wall material to protect it from tidal damage. These sulfated polysaccharides also help reduce inflammation, oxidative stress, and free radicals, making them a suitable candidate for treating Neurodegenerative disorders like Alzheimer's [2]. Some chemical components like lignans, polysaccharides, triterpenes, alkaloids, and saponins show anti-Alzheimer actions through their multitarget mechanisms [3].

6.2 STRUCTURE OF POLYSACCHARIDES

Polysaccharides are complex carbohydrates made up of repeating units of monosaccharides (simple sugars) linked together by glycosidic bonds. They are the largest and most abundant group of carbohydrates found in nature. The structure of polysaccharides can vary depending on the type of monosaccharides involved, the arrangement of glycosidic bonds, and the presence of branching.

Here are some common structural features of polysaccharides:

1. **Monosaccharide Units:** Polysaccharides are composed of monosaccharide units such as glucose, fructose, galactose, or mannose. These monosaccharides can be in different forms, such as alpha or beta configurations, which affect the structure and properties of the polysaccharide.
2. **Glycosidic Bonds:** Monosaccharide units are linked together through glycosidic bonds, which form between the hydroxyl group of one monosaccharide and the anomeric carbon of another monosaccharide. The type and position of the glycosidic bonds determine the specific polysaccharide structure.

3. **Linear or Branched Structure:** Polysaccharides can have a linear or branched structure. In linear polysaccharides, the monosaccharide units are joined in a straight chain. In branched polysaccharides, additional monosaccharide units branch off from the main chain.
4. **Homopolysaccharides and Heteropolysaccharides:** Homopolysaccharides consist of a single type of monosaccharide repeated in the chain, while heteropolysaccharides contain more than one type of monosaccharide.

Examples of polysaccharides:

1. **Glycogen:** An animal polysaccharide similar to starch but with more frequent branching. It is the primary storage form of glucose in animals, particularly in the liver and muscles.
2. **Cellulose:** A structural polysaccharide found in the cell walls of plants. It consists of linear chains of glucose units linked by beta-1,4-glycosidic bonds. Cellulose is not digestible by most animals but serves as a source of dietary fiber.
3. **Chitin:** A polysaccharide found in the exoskeletons of arthropods (e.g., insects, crustaceans) and the cell walls of fungi. It is composed of N-acetylglucosamine units joined by beta-1,4-glycosidic bonds.
4. **Hyaluronic Acid:** A heteropolysaccharide found in the connective tissues of animals. It consists of alternating units of glucuronic acid and N-acetylglucosamine linked by beta-1,3 and beta-1,4-glycosidic bonds.
5. **Starch:** A plant polysaccharide composed of glucose units joined by alpha-1,4-glycosidic bonds in a helical structure. It serves as an energy storage molecule in plants.

These are just a few examples, and there are many other types of polysaccharides with diverse structures and functions found in nature. The specific arrangement of monosaccharides and glycosidic bonds gives each polysaccharide its unique properties and biological roles [4–7].

6.3 MECHANISM OF ACTION OF POLYSACCHARIDES

Reactive oxygen species produced by different metabolites are responsible for the degeneration of nerve cells as they regulate the functions of different

biological molecules like DNA, RNA, proteins, and lipids present in the nerve cells. As the level of reactive oxygen species increases in our body, it eventually destroys biomolecules like neurons. Bioactive polysaccharides counteract free radicals and reactive oxygen species by enhancing many antioxidant enzymes and regulating stress-related signaling events by adjusting and controlling gene expression [8]. Various factors such as trauma, infection, and toxins cause uncontrolled or protracted neuroinflammation of the neurons, which disturbs the homeostasis of the brain, one of the key factors responsible for neurodegenerative disorders. Microglial cells in their overactivated state produce proinflammatory cytokines like IL-6, IL-8, etc., which act as targets for the polysaccharides to regulate and reduce during the treatment of Alzheimer's. Under normal physiological conditions, the rate of apoptosis of neuronal cells is approximately zero, but due to an increase in apoptosis-related proteins, apoptosis becomes the key factor responsible for neuronal death during neurodegenerative disorders. Polysaccharides protect the neurons from this apoptosis by maintaining the internal environment of the mitochondria and blocking the caspase cascade reaction. Polysaccharides also increase anti-apoptotic proteins, decrease pro-apoptotic proteins, and also activate the Akt-MTOR pathway. Polysaccharides also inhibit the cytotoxicity induced by acidic amino acid glutamate, which is also a key factor contributing to neurodegeneration [9]. It has been discovered that there is a synergistic effect between the tau proteins and Amyloid β, in which the Amyloid β precipitation leads to a cascade of reactions leading to misfolding of tau proteins, which cause lesions in the entire neuronal circuit. It was then speculated that Chinese herbs containing polysaccharides target BACE1, which could inhibit the deposition of Amyloid β and in turn tau protein misfolding in the brain. Currently, the medicines used in the market have single targets in the treatment of Alzheimer's disease, but a multi-target approach is more stable and efficient, and can act on multiple causative agents at the same time [10]. Several terpenoids, flavonoids, coumarin, and polyphenol compounds extracted from various Chinese herbal medicines have shown BACE1 and AChE inhibitory activity [11].

6.4 POLYSACCHARIDES IN THE TREATMENT OF ALZHEIMER'S DISEASE

6.4.1 KOREAN RED GINSENG

The non-saponin fraction with rich polysaccharides (NFP) was isolated to study its action on the various parameters of Alzheimer's brain. Initially,

the proteomic study was carried out and it was found that differentially expressed proteins are largely involved in cellular organization, assembly, maintenance, and growth. Korean Red Ginseng increased the formation of dendritic spines, neurogenesis, cell movement in neurons, and myelination of neurons as observed in the proteomic study. NFP from Korean Red Ginseng was administered for 3 weeks (50 mg/kg) to a 5.5-month-old 5XFAD mouse which was an analysis of NFP activity on the size of Amyloid β deposit and was concluded that there was a significant reduction in the size of Amyloid β deposit in the brain of Alzheimer-induced mice. Korean Red Ginseng NFP extracts also reduced Amyloid β deposit-induced neuro-inflammation in the 5XFAD mice. It was also observed that there was a significant reduction in neuronal death induced by both aging and Amyloid β plaques in Alzheimer-induced mice. Immunofluorescence staining showed that there was amelioration in mitochondrial dysfunction and also balanced the mitochondrial dynamics which were disturbed due to Amyloid β overexpression in the mice brain. In the hippocampal region, there was an increase in non-mitochondrial respiratory cells which was due to the mitigation of Amyloid β by the NFP. Also, there was not only protection of the hippocampal neurons but also neurogenesis of the hippocampal neurons. NFP administration to the diseased mouse also enhanced cognitive function. Hence, in conclusion, NFP extract from Korean Red Ginseng could be a multitarget approach in the treatment of Alzheimer's disease [12].

6.4.2 INONOTUS OBLIQUUS

In a study conducted by Yanqiu Han and colleagues, *Inonotus obliquus* polysaccharide (IOPS) was extracted and purified to study its anti-Alzheimer's properties. Glutamate is an excitotoxic neurotransmitter that causes neurodegeneration in neuronal diseases like Alzheimer's. During L-Glutamate-induced HT22 cell death, there is subsequent fusion between glutamate and mitochondria which leads to an increase in Reactive Oxygen Species and hence oxidative stress. Mitochondrial dysfunction activates a feedback loop system that exacerbates mitochondrial dysfunction. This dysfunction occurs due to an imbalance between the levels of Bax and Bcl-2 which further activates the caspase-3 pathway. Polysaccharides present in IOPS have the capability of protecting against the neurotoxicity induced by L-Glutamate by inhibiting mitochondrial dysfunction. IOPS also regulates Nrf2 which is a modulator of about 250 genes involved in

cellular homeostasis during oxidative stress. Nrf2 also protects against the oxidative challenges encountered during the treatment of Alzheimer's [13]. In an APP/PS1 mouse model consisting of the PS1 mutant gene, there was an abnormally increased level of amyloid 1–42 levels that caused a decrease in learning and memory capabilities and deposition of senile plaque and tau proteins. IOPS (260 mg/kg, 0.1 ml/10 g of body weight) through their neuroprotective action and Nrf2 pathway was able to reduce the aggregation of tau proteins and senile plaques, thereby treating Alzheimer's disease [14].

6.4.3 ANGELICA SINENSIS

In a recent study, 60 Sprague-Dawley rats were taken and divided randomly into groups. The mice group affected with Alzheimer's was infused with Amyloid β_{25-35} and the treatment groups received Donepezil HCL and *Angelica Sinensis* polysaccharide extract (ASP). During the Morris water test, the mice group receiving ASP had a shorter residence time in the last quadrant as compared to the other groups, indicating that ASP could ameliorate the impairments linked with the spatial learning events. ELISA test also confirmed that ASP maintains the normal secretions of neurotransmitters like Acetylcholine and ChAT in the mouse brain [15]. ASP (50 mg/kg) also reduced neuroinflammation by decreasing the levels of IL-1β, IL-6, and TNF-α in the brain. It was also observed that in the CA3 and DG hippocampal regions, there were positive neurons as observed by Nissl staining, indicating that ASP protected against neuronal damage. ASP also caused a reduction in the expression of Bcl-2, Bax, and caspase-3 as it inhibited neuronal apoptosis. The activation of BDNF/TrkB/CREB pathway further indicated that ASP inhibited the development of brain senility, increased neurogenesis, inhibited neuronal apoptosis induced by Amyloid β plaques, and regulated free radical metabolism [16].

6.4.4 SCHISANDRA CHINENSIS FRUCTUS

Schisandra chinensis (SC), commonly called "Wuweizi" in Chinese, is a traditional Chinese medicine with astringent characteristics that tranquilize the mind, nourish the kidney, and calm the heart. According to Chinese medicine theory, the brain is closely related to the five viscera. Elderly

people often have insufficient body fluids and kidney problems, which can lead to forgetfulness or dementia. Chinese medicines are also advantageous as they have multiple roles to play in disease treatment. Polysaccharides, also known as immune polysaccharides, possess anti-inflammatory properties by suppressing pro-inflammatory cytokines such as cytokines, lipid metabolites, and free radicals [17]. SC polysaccharides (260 mg/kg) were found to improve short-term learning memory and cognitive capacity, as observed in the Morris water maze test. Biochemical analysis further indicated that SC polysaccharides reduced the activation of astrocytes and microglia, which are responsible for central neuro-inflammation, as shown by reduced levels of IL-1β, IL-6, and TNF-α. SC polysaccharides also reversed histopathological changes in the hippocampal region by downregulating the P38/ERK/JNK pathway. Research also suggested that SC polysaccharides reduced the deposition of Amyloid β plaques, making it a potent traditional Chinese medicine in the treatment of Alzheimer's disease [18].

6.4.5 LYCIUM BARBARUM

It is a traditional Chinese medicine with multitudinous components such as flavonoids, polysaccharides, taurine, betaine, cerebroside, and vitamins. Many studies have shown that polysaccharides present in *Lycium barbarum* (Lb) aqueous extract prevent memory and neurogenetic impairment in scopolamine-treated rats, improve cellular immunity, and are neuroprotective in nature against homocysteine-induced toxicity [19]. Mice infused orally with Lb (50 mg/kg or 20 g of mouse body weight) reached the target quadrant in a shorter period compared to the model mice and hence ameliorated the cognitive functions. Also, the number of Amyloid β plaques was half compared to the model mice, and there was also a reduction in the area covered by the plaques. In the mice treated with Lb polysaccharides, there were a greater number of BrdU/NeuN double-positive cells in the hippocampal region, which is indicative of neurogenesis and neuronal proliferation. The hippocampus plays a crucial role in memory and the spatial learning process; during Alzheimer's, this neuronal circuit gets damaged. The synaptic plasticity at the CA1 stratum radiatum was also improved with the administration of Lb aqueous polysaccharide extract [20]. Table 6.1 gives us an illustrative view of the polysaccharides used in neuroprotection.

TABLE 6.1 Polysaccharide Studies Used in Neuroprotection

Polysaccharide	Dose	Macroalgae	Bioactivity	Model	Experimental	References
Fucoidan	1–50 µg/ml	*F. vesiculosus*	Energy production or biogenesis of mitochondria.	*In-vitro*	Metal chelating activity and ABTS•+, DPPH•, •OH scavenging.	[13]
Fucoidan	3.125–100 µg/mL	*F. vesiculosus*	Anti-aggregation $A\beta_{1-42}$	*In-vitro*	H_2O_2 or $A\beta_{1-42}$ treated PC-12 cells (parameters assessed, neurite outgrowth, apoptosis, and viability).	[21]
Porphyran	25 and 50 mg/kg	*P. capensis*	Anti-apoptotic	*In vivo*	Male C57BL6 mice model of PD induced by MPTP (parameters assessed: behavioral patterns and body weight ratio).	[22]
K-carrageenan	0.01–1.0 mg/mL	*H. musciformis*	Anti-apoptotic	*In-vitro*	SH-SY5Y cells treated by 6-OHDA (parameters assessed apoptosis, H_2O_2 levels, mitochondrial potential, and cell viability).	[23]

6.4.6 CODONOPSIS PILOSULA

It is an old Chinese medicine that is neuroprotective in nature, attenuates tau proteins, and increases synaptic proteins including PSD95 and synaptotagmin. The beta site of Amyloid precursor protein cleaving enzyme 1 (BACE1) is responsible for the breakdown of Amyloid Precursor Protein (APP) to APP β, which is a limiting process in the generation of Amyloid β plaques in Alzheimer's disease. Polysaccharides of *Codonopsis pilosula* (CPP, 300 mg/kg) inhibit BACE1 and hence reduce Amyloid β plaque formation. It also contains other complex components like alkaloids, phytosterols, essential oils, and polyacetylenes which possess antioxidant, antimicrobial, and immunoenhancing properties. CPPs increased the recognition in mice of new objects and attenuated cognitive deficits in CPP-treated mice. Golgi staining reported that there was a significant reduction in dendritic and mushroom-like spines, which is indicative of restoration of synaptogenesis and synaptic plasticity. CPP also reduced the levels of Amyloid β plaques$_{40, 42}$ and senile plaques, relieved Amyloid β plaques induced toxicity, and reduced the levels of active recombinant human β Secretase, which all indicated that CPP attenuated Alzheimer's disease [25].

6.4.7 ANNONA MURICATA

Leaves of *Annona muricata* are a plant herb that contains various polysaccharides such as galactose, glucose, mannose, fucose, glucosamine, and galactosamine. They have shown an increase in the activity of the antioxidant enzyme superoxide dismutase (SOD), which reduces the reactive oxygen species to hydrogen peroxide and malondialdehyde to less harmful compounds [26]. Antioxidants are compounds that terminate the oxidative chain reaction by eliminating their intermediates, thereby reducing the damage caused to the neuronal tissues. *Annona muricata* polysaccharides (AMP) have antioxidant activities that scavenge free radicals present in the hippocampal neuronal cells. There was a notable reduction in late apoptosis, nuclear fragmentation, accumulation of cells in the G1 phase, and morphological damage, which is indicative of decreased neuronal death. Mitochondrial membrane potential dysfunction, which plays a pivotal role in neurodegenerative diseases and excessive calcium loads, was also normalized upon treatment with AMP. Neuronal cell death shifts to necrosis as neurons mature, AMP restores cytosolic cytochrome c, Bax to normal, which in turn blocks the mitochondrial

apoptotic pathway. AMP reduced neurotoxicity by inhibiting the PI3K/AKT pathway and reducing the phosphorylation of MAPKs and nuclear translocation of NF-κB. Another biochemically prominent indicator of the treatment of Alzheimer's disease was an increase in nuclear levels of Nrf2, NQO-1, and HO-1 (cytoprotective genes) [27].

6.4.8 MARINE POLYSACCHARIDES

Due to the presence of many unique and undiscovered chemical components in water compared to land, marine polysaccharides are a booming area in the treatment of Alzheimer's disease. Chemical compounds such as polysaccharides, alkaloids, amino sulfonate, diterpenoids, and carotenoids found in marine habitats possess 10 times more biological activities compared to terrestrial ones. Polysaccharides are high-molecular-weight polymeric structures of carbohydrates that are linked through glycosidic linkages [28].

Fucoidan is a complex polysaccharide that is extracted from many marine invertebrates and brown seaweeds. Chemically, it is made up of L-fucoses and sulfate groups that possess not only anti-Alzheimer properties (through the improvement of cognition deficiency caused by Amyloid β_{1-40}) but are also anticoagulant, anti-inflammatory, antiviral, and resistant to oxidation [29]. One α (1→3) adds the fucose residue to the main polysaccharide chain, and a second α chain alternating between (1→3) and (1→4) adds sulfate residues to the main carbohydrate backbone structure. Fucoidan blocks the activity of enzymes caspases 3 and 9, and Amyloid β, which are responsible for neuronal cell death. It also reduces the calcium load present in the environment of dopaminergic neurons, which is responsible for accelerated neuronal apoptosis. Fucoidan also reduces toxicity by inhibiting the β-amyloid protein present on the protein kinase C, increasing mitochondrial activity, reducing the release of lactate dehydrogenase, reducing the expression of pro-apoptotic protein Bax, and enhancing the expression of anti-apoptotic protein Bcl-2, all of which promote neuroprotection and reduce apoptosis of neurons [30].

Chitosan, also known as deacetylated chitin, is found in the cell wall of many crustaceans and fungi. It is a copolymer of N-acetyl-D-glucosamine that has significant immuno-regulatory, anti-apoptotic, antibacterial, and oxidative resistance activities [31]. In Alzheimer's disease, chitosan plays a protective role by regulating the activity and expression of the BACE-1 enzyme, which is responsible for the production of amyloid β and is also an inhibitor of Acetylcholinesterase in its oligomer form. It also protects the neurons from apoptosis through its neuroprotective activities [32].

6.4.9 MICROBIAL POLYSACCHARIDES

Microbial polysaccharides are high molecular weight (Mw) carbohydrate polymers produced by microorganisms, namely bacteria, yeast, fungi, and microalgae. Some of these polysaccharides are intracellular in nature as they accumulate as carbon and energy reserves (e.g., glycogen) in the cytoplasm of cells, providing structural stability to the cells (e.g., chitin). The extracellular polysaccharides are produced by cells that form a capsule closely associated with the cellular surface (capsular polysaccharides) or as a slime loosely associated with the cell surface (exopolysaccharides). These polysaccharides can be used as structuring agents or as biologically active molecules [33]. Exopolysaccharides have various applications in controlled release, adjuvants, vaccines, and diagnostic imaging systems. Microbial exopolysaccharides of bacterial origin offer advantages such as lubricity, viscoelasticity, ionic strength, geling, and cross-linking [34]. These properties make microbial polysaccharides suitable for use as replacement structures in areas such as the urinary tract, windpipe, and cardiovascular system. Due to their water-holding capacities, microbial polysaccharides can be used as thickening, emulsion stabilizing, flocculating, and film-forming agents in biomedical fields. An important characteristic of microbial polysaccharides is that they are biodegradable and biocompatible [35].

6.4.10 BACILLUS AMYLOLIQUEFACIENS

Bacillus amyloliquefaciens is a bacterium of marine origin that contains two major exopolysaccharides: D-galactose and D-mannose. It has been reported that marine polysaccharides of *Bacillus amyloliquefaciens* reduce aggregation of β-amyloid protein, which reduces convulsions and improves memory retention in Alzheimer-induced mice. Biochemical tests indicate that it also has a negative effect on the Acetylcholinesterase activity, which is primarily responsible for hippocampal atrophy and the progression of disease conditions like Ataxia, Parkinson's, Senile dementia, and Alzheimer's [36]. Treatment with polysaccharides of *Bacillus amyloliquefaciens* caused a reduction in latency as well as the transverse period of mice in the jumping box and rectangular maze test. After infusion of polysaccharide, it was also found that senile plaques almost disappeared within 24 hours, which is prominent in Alzheimer's disease. These activities of *Bacillus amyloliquefaciens* act as a breakthrough treatment of neurodegenerative diseases caused by oxidative stress compared to the commercially available medicines.

6.4.11 BACILLUS SUBTILIS

Bacillus subtilis contains a novel exopolysaccharide (EPSR4) which is a *β*-glycosidic sulfated heteropolysaccharide that is constituted of glucose, rhamnose, and arabinose monosaccharides in the ratio of 5:1:3 [37]. It also has 97.6% free radical scavenging activity against DPPH and hydrogen peroxide, lipoxygenase, and cyclooxygenase inhibitory activity. They possess exclusive properties due to their ability to adapt to extreme conditions and can be produced in bioreactors under controlled conditions. Polysaccharides from *Bacillus subtilis* further also suppressed T-cell activation and immune responses mediated by T-cells [38]. EPSR4 has considerable inhibitory activity against Acetylcholinesterase and is also a cyclooxygenase inhibitor which reduces neuroinflammation associated with neurodegenerative disorders. It also acts as a strong inhibitor against lung cancer and human hepatoma cell lines [33, 39]. The various ongoing clinical trials for polysaccharides are shown in Table 6.2 [40].

6.4.12 CHALLENGES AND FUTURE OPPORTUNITIES

Chinese and Korean scientists have been using polysaccharides from red, green, and brown algae as medicines because of their diverse characteristics such as anti-coagulant, antioxidant, anti-inflammatory, anticancer, antiviral, and anti-cancer. The sulfated chemical components present in them are mainly responsible for these properties, and the non-sulfated ones when treated with sulfur proved to be powerful antioxidants in nature. In several studies, it has been found that the cells treated with the sulfur-attached polysaccharides had longer cell viability compared to the untreated ones. The traditional medicines used in the treatment of Alzheimer's do not target the amyloid beta plaques and in some cases exacerbate the situation even more. There has been a more inclination towards the use of herbal/natural medicines like polysaccharides in the treatment of neurodegenerative disorders. But the challenge with the use of herbal medicines is their targeting and passage across the various membrane barriers. To overcome these, the sulfated polysaccharides are reduced to nano-size and attached to carriers which enhance the overall efficiency of these polysaccharides being used in the treatment of multivariate diseases [41]. Chitosan and its derivatives have been recently used in the passive targeting of drugs across the Blood-Brain Barrier as chitosan is positively charged in nature and the brain is

TABLE 6.2 Ongoing Clinical Trials for Polysaccharides

Title	Disease/Condition	Plant Preparation or Compound	Initial Date	Clinical Trial Identifier
Recovering damaged cells for sequelae caused by COVID-19, SARS-CoV-2 (sequelae).	Several sequelae from COVID infection including anxiety, depression, and post-infectious Parkinsonism.	Several plant preparations. PurWet includes Poria and Glycyrrhizae Radix, among others; Smoliv includes Curcumae Radix and Paeoniae Radix rubra, among others PurClo contains Curcumae Radix, among others; PurInf contains Scutellariae Radix and Gardeniae Fructus.	March 2021	NCT04846010
Non-pharmacological intervention for preclinical Alzheimer's disease.	Alzheimer disease/ cognitive decline.	Functional foods with main compositions of ginsenoside, marine collagen peptide, and green tea polyphenols.	April 2019	NCT04279418
Enoxolone in major depression-biomarker-outcome relationship.	Unipolar depression	Enoxolone (pentacyclic triterpenoid aglycone metabolite of glycyrrhizin).	September 2022	NCT05570110
RCT of adjunctive curcumin and the Meru Health Program.	Depression	Curcumin	February 2021	NCT04744545
An exploratory investigation of a CBD supplement's impact on sleep, focus, and stress.	Anxiety/mood/sleep fear/ stress/low.	Organic broad spectrum Hemp extract 35 mg bio-terpene complex 52 mg palm monoglycerides organic Hemp seed oil, curcumin (turmeric root) essential oil, clove bud oil, black pepper berry essential oil.	February 2022	NCT05518019
Safety and target engagement of *Centella asiatica* in cognitive impairment.	Alzheimer's disease/mild cognitive impairment.	*Centella asiatica*	November 2022	NCT05591027
A phase I/II study of PDC-1421 for treating depression in cancer patients.	Major depressive disorder.	PDC-1421 capsule is a botanical investigational new drug containing the extract of Radix Polygalae (*Polygala tenuifolia*) as active ingredient.	October 2022	NCT03833206
PDC-1421 treatment in adult patients with ADHD.	Attention-deficit hyperactivity disorder (ADHD).	PDC-1421 capsule	April 2022	NCT05202327

negatively charged. Active and stimuli-responsive polysaccharides are the newly emerging fields of targeted drug delivery systems. In conclusion, polysaccharides are widely used in the treatment of Alzheimer's disease, but additional research is required in the field of toxicity, efficacy, mechanism of action, and human efficacy trials [42].

KEYWORDS

- **Alzheimer's disease**
- **antioxidants**
- **chitosan**
- **herbal medicines**
- **neurodegenerative disorders**
- **neuroprotective activities**
- **nutraceuticals**
- **polysaccharides**

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CHAPTER 7

Neuro-Protective Role of Vitamin D in Alzheimer's Disease

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ABSTRACT

The number of cases of Alzheimer's disease (AD) is increasing, especially in the geriatric age group, and one of the most common and significant causes is a chronic deficiency of Vitamin D. Undoubtedly, the area is still not explored much, and we have very little information regarding the effect of vitamin D on the pathology of AD. However, studies have proven the relationship of vitamin D with neurotrophin, neurotransmission, neuroprotection, and neuroplasticity, which shows the importance of vitamin D in the progression of AD. The studies have also shed light on increased inflammatory factor secretion and elevated glial activation due to the deficiency of Vitamin D, which results in rising levels of amyloid precursor protein (APP) and β-site APP cleavage enzyme 1 (BACE1), further resulting in the elevated production and deposition of Aβ. Phosphorylation of Tau at Thr181, Thr205, and

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Ser396 is significantly elevated with the increase in cyclin-dependent kinase 5 (CDK5), which escalates the production of glycogen synthase kinase 3α/*β* (GSK3α/*β*). Studies have also observed synaptic dystrophy and neuronal loss as a result of vitamin D deficiency. Vitamin D helps in slowing down the process of free radical formation in the brain. It acts as a charioteer for the brain by helping to regulate the cellular processes of the brain. It helps in maintaining the signaling of neurotransmitters across the dopaminergic pathways. The main characteristic of Alzheimer's disease is the formation of amyloid plaques, and vitamin D has the potency of clearing these plaques. Vitamin D also plays a key role in improving the cognitive mental state of some patients. Data has shown that countries with below-average sunlight exposure or people who have very limited exposure to sunlight have a high fatality rate due to AD caused by VD.

7.1 INTRODUCTION

Alzheimer's disease (AD) is one of the main reasons for the increased rate of dementia. Progressively decreasing memory and cognitive deficits are two main indicative factors of AD [41]. AD is a neurodegenerative disorder that is characterized by extracellular fibrillar *β*-amyloid protein (A*β*), which is responsible for the formation of senile plaques (SPs) as it gets deposited in voids [33]. Intracellular fibrillary tangles are seen in the tau proteins, another factor considered for diagnosing AD. Tau protein is hyperphosphorylated, due to which intracellular neurofibrillary tangles are formed. There is noticeable amnesiac forgetfulness seen in patients with AD [49]. Amnestic cognitive impairment is used to manifest AD, but a few percent of AD patients are deprived of this indicator. Neuron loss is another main pathological indicator of AD [14].

According to WHO, AD is a condition with neurological degeneration resulting in brain cell death and shrinkage of brain size; it progressively destroys brain cells, ultimately causing brain atrophy [4]. It is also responsible for impairing the ability and capacity of humans to function independently. Persistent loss in thinking, decreased social abilities, lesser interaction with people, difficulty in maintaining a conversation, and response towards the environment decrease; in extreme cases, the condition worsens, and the patient may experience hallucinations, cognitive deceleration, disorientation, mood and behavior changes, increased confusion regarding the events happening around, loss of record of time and place, and may feel suspicious about loved ones [8].

In general, memory loss can progress enough to interfere with daily tasks and make it very difficult for patients to survive. As the condition worsens and memory loss deepens, there is a visible change in speech. Patients with AD may have difficulty forming sentences, resulting in speech difficulties. Difficulty in swallowing and walking has also been observed [54].

It has been observed that people with such a problem usually deny the condition and make it harder for the family members to recognize the problem. An early diagnosis can not only slow down the condition but is also responsible for opening the gates for numerous treatment options [46].

It was recently seen that several fat-soluble vitamins such as Vitamin A, provitamin A beta-carotene, Vitamin D3, Vitamin K, and Vitamin E are found in very low amounts in AD patients. Vitamin D affects around 90% of the elderly population [23].

Vitamin D is considered a neuroactive steroid. The data collected to date suggests that Vitamin D should be included in the broader family of neuroactive steroids, as it plays a crucial role in brain development [50]. Numerous studies have demonstrated that modifying the concentration or function of ligands can lead to significant changes in brain development and the repair of brain cells. While it is well-established that Vitamin D is naturally present in the human brain, a definitive pathway for its role has not been identified yet [63].

Understanding the precise changes in the weakening of memory due to deficiency of Vitamin D is quite complex. This topic remains relatively unexplored, but a decade ago, there were suggestions that Vitamin D could be referred to as the "forgotten neurosteroid" [64]. Many studies have proved that vitamins have a great impact on CNS signaling. Few of these studies have also given convincing evidence that Vitamin D is much required for normal brain homeostasis and helps the brain's overall development. A deficiency of Vitamin D is not only responsible for weaker bones but is also responsible for increasing psychiatric conditions. Vitamin D, also known as the sunshine hormone (Figure 7.1), has a diverse effect on the working of the CNS [57]. Vitamin D is responsible for the progression of AD and is somehow linked to all sorts of neurodegenerative disorders. Not receiving sufficient Vitamin D may double the risk of developing neurodegenerative disorders. The hypothesis suggests that just by increasing the dosage of Vitamin D from 25 nmol/L to 50 nmol/L, we can prevent around 17% of potential cases. Vitamin D deficiency affects not only psychological behavior, motor functions, perception, and sensory-motor gate [56].

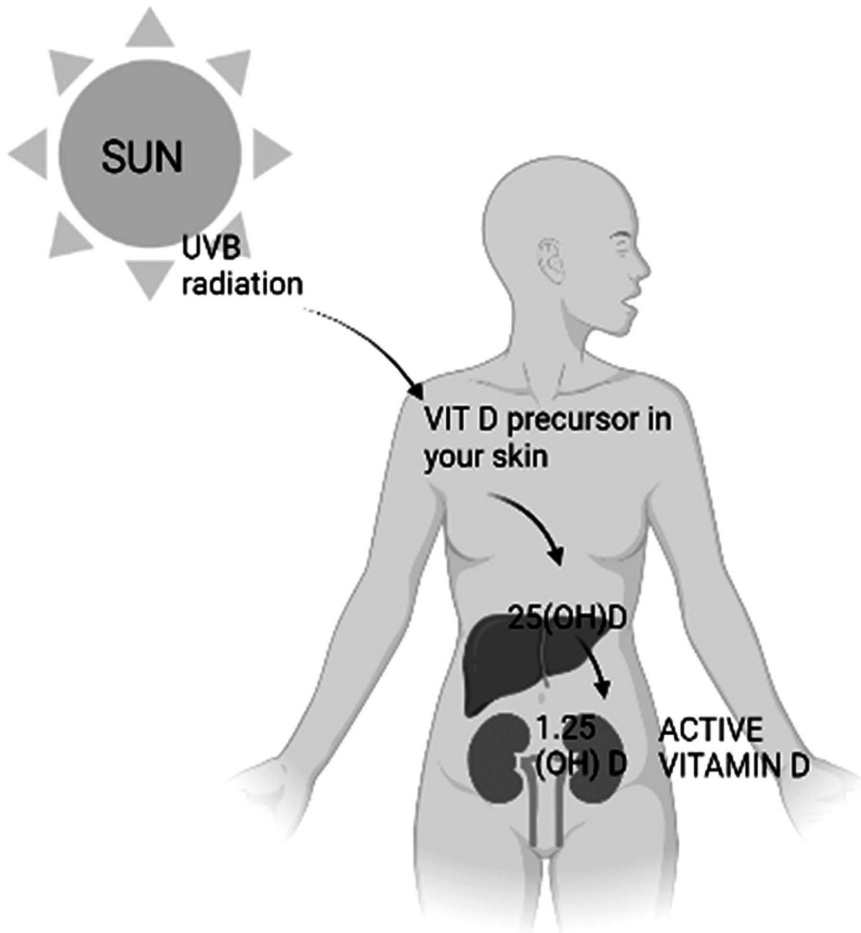

FIGURE 7.1 Conversion of vitamin D into an active form.

7.2 IMPACT OF VITAMIN D DEFICIENCY ON NEURODEGENERATION

When an individual's blood vitamin D level falls below 30 nmol/L, it is categorized as a deficiency. Due to a deficiency of Vitamin D in the body, a very noticeable disturbance in the synthesis and regulation of neurotransmitters is usually seen [3]. Consequently, these disturbances lead to the manifestation of various symptoms, including but not limited to depression, anxiety, panic attacks, eating disorders, chronic pain, and adrenal

dysfunction (Figure 7.2). The disruption in the synthesis and regulation of neurotransmitters, specifically affecting dopamine beta-hydroxylase activities, is accountable for these effects [62]. Ascorbic acid is unable to get converted into dehydroascorbic acid; similarly, dopamine remains in its form and does not get converted into noradrenaline, which is responsible for the accumulation of ascorbic acid and dopamine in the brain, resulting in a contribution to increasing the inflammatory oxidative stress, lipid peroxidation, mitochondrial dysfunction, formation, and accumulation of APP and tangles. As the formation and accumulation of APP and tangles increase, it will start affecting neuron cells. The proliferation of degenerative neuron cells leads to the progressive deterioration of brain cells, known as neurodegeneration [13].

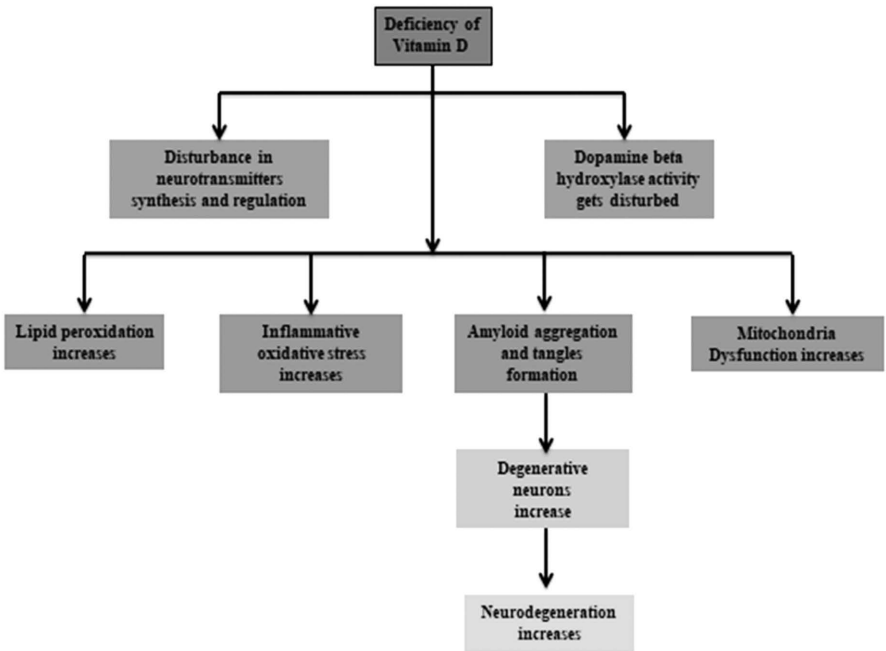
Deficiency of Vitamin D
Disturbance in neurotransmitters synthesis and regulation
Dopamine beta hydroxylase activity gets disturbed
Lipid peroxidation increases
Inflammative oxidative stress increases
Amyloid aggregation and tangles formation
Mitochondria Dysfunction increases
Degenerative neurons increase
Neurodegeneration increases

FIGURE 7.2 Deficiency of vitamin D affecting neurodegeneration.

Low Vitamin D levels are responsible for the induction of Aβ generation and will also reduce enzyme-mediated degradation. Since Vitamin D deficiency hinders the clearance of Aβ out of microglial cells, it will start accumulating and become a reason for memory impairment [43].

7.3 INVOLVEMENT OF VITAMIN D IN PATHOGENESIS OF AD

7.3.1 NEUROTRANSMITTER SYNTHESIS AND RELEASE

The hippocampus is one of the brain areas that contain Vitamin D receptors (VDRs), which are important in learning and memory. Acetylcholine, dopamine, and glutamate are three neurotransmitters that are important for memory and cognition and can be affected by Vitamin D activation of these receptors [61].

7.3.2 NEUROPROTECTION AND ANTI-INFLAMMATORY EFFECTS

It has been discovered that Vitamin D has neuroprotective properties that can assist in maintaining memory and cognitive function. It might lessen oxidative stress and stop the brain from producing inflammatory chemicals, safeguarding neurons from harm and enhancing overall brain health [55, 26].

7.3.3 MODULATION OF CALCIUM SIGNALING

Calcium signaling, which is essential for neural transmission and synaptic plasticity (the capacity of synapses to grow stronger or weaker with time), is regulated by Vitamin D in a critical way. The regulation of calcium entry into neurons, which is crucial for the processes involved in memory formation and synaptic plasticity, is aided by Vitamin D [60].

7.3.4 PROMOTION OF NEUROTROPHIC FACTORS

Brain-derived neurotrophic factor (BDNF) and other neurotrophic factors can be produced and released in response to Vitamin D. For instance, BDNF is involved in synaptic plasticity and the creation of new connections in the brain, which are essential for learning and memory. Neurotrophic factors promote the survival, development, and differentiation of neurons [38].

7.3.5 REGULATION OF GENE EXPRESSION

The expression of genes involved in neurogenesis (the growth of new neurons), neuronal differentiation, and synaptic function can all be affected by Vitamin D in brain cells. Vitamin D may improve memory-related functions and support cognitive function by modulating gene expression [30].

7.3.6 VITAMIN D RECEPTOR (VDR)

The Vitamin D receptor, a nuclear receptor found in neurons and glial cells, is where Vitamin D exerts its effects. The activation of VDR by Vitamin D results in a series of molecular occurrences that control gene expression and have an impact on cellular functions important for memory development and maintenance [44].

7.3.7 BDNF-TRKB PATHWAY

A molecule called brain-derived BDNF helps neurons, especially those involved in memory processes, grow, survive, and operate. The TrkB receptor interacts with Vitamin D to boost neuronal survival, synaptic plasticity, and the growth of new connections – all of which are essential for memory enhancement. Vitamin D can increase the expression of BDNF [32].

7.3.8 NMDA RECEPTOR AND SYNAPTIC PLASTICITY

The synaptic plasticity that underlies learning and memory involves the N-Methyl-D-Aspartate (NMDA) receptor. To increase synaptic plasticity and facilitate the strengthening of synaptic connections during memory formation, Vitamin D affects the production and function of NMDA receptors [35].

7.3.9 CALCIUM SIGNALING

Calcium signaling is crucial for many neural activities, and Vitamin D is involved in preserving calcium homeostasis. Adequate calcium signaling, which is necessary for synaptic transmission, neurotransmitter release, and synaptic plasticity – all of which have an impact on memory improvement – is facilitated by adequate Vitamin D levels [27].

7.3.10 ANTI-INFLAMMATORY PATHWAYS

Memory and cognitive function may suffer from chronic inflammation. By modifying inflammatory signaling pathways, such as NF-κB and cytokine production, Vitamin D has anti-inflammatory effects. Vitamin D may defend against memory loss and boost memory by lowering neuroinflammation [7].

7.3.11 OXIDATIVE STRESS PATHWAY

Oxidative stress can harm cells and decrease memory performance. Vitamin D has antioxidant qualities and can influence oxidative stress pathways, such as the activation of antioxidant enzymes and the decrease of reactive oxygen species (ROS), defending neurons from oxidative damage and assisting in memory enhancement [9].

7.4 VITAMIN D METABOLISM AND ITS MECHANISMS OF ACTION IN THE CENTRAL NERVOUS SYSTEM

When exposed to sunshine, the skin first produces Vitamin D; it can also be consumed through dietary sources. It is transformed metabolically into calcitriol (1,25-dihydroxy vitamin D), which is the active form, in the liver and kidneys. The enzymes 25-hydroxylase and 1-hydroxylase are involved in the strictly controlled conversion of Vitamin D to calcitriol. Calcitriol must bind to the Vitamin D receptor (VDR) found in target tissues such as the brain to have an effect. Various parts of the brain involved in neurotransmission contain Vitamin D and its receptors [12]. Neurotransmitters including acetylcholine, dopamine, and glutamate, among others, can be affected by calcitriol's effects on their synthesis and release. The metabolism of Vitamin D affects memory, mood management, and cognitive function via regulating neurotransmitter levels. In the brain, Vitamin D demonstrates neuroprotective qualities. It aids in lowering oxidative stress and inflammation, which can be harmful to the health of neurons [1]. To prevent pro-inflammatory chemicals from being released and to maintain the survival of neurons, Vitamin D stimulates the production of antioxidant enzymes and suppresses their activity. The preservation of calcium homeostasis is one of Vitamin D's principal functions in the brain. Numerous neural functions, such as neurotransmitter release, synaptic plasticity, and neuronal excitability, depend on calcium signaling. In order to maintain adequate calcium levels for neuronal activity, Vitamin D improves calcium absorption in the gut and controls calcium transport across cell membranes [40]. Gene expression in the brain is regulated as a result of calcitriol activating the VDR. It affects the transcription of genes involved in the creation of neurotransmitters, synaptic plasticity, neurotrophic factor, and other essential processes for brain function. The metabolism of vitamin D can affect cognitive

functions such as synaptic connection, neuronal development, and gene expression. The brain's immunological responses are modulated by Vitamin D metabolism [16, 17, 28].

Calcitriol affects the activation and operation of immune cells inside the central nervous system by controlling the expression of genes involved in immune function. Vitamin D metabolism can support brain health maintenance and safeguard against neuroinflammatory processes by regulating immune responses [36, 44].

A study has shown that a Vitamin D-enriched diet seems to be very effective in decreasing amyloid plaque formation and is also responsible for a visible decline in Aβ peptide. This decrease leads to reduced inflammation and an increase in nerve growth factor (NGF) [51].

7.5 GENETIC FACTORS RESPONSIBLE FOR THE PREVALENCE OF ALZHEIMER'S DISEASE

Numerous studies have investigated the association between Vitamin D-related genes and AD. Variations in genes involved in Vitamin D metabolism and signaling pathways have been implicated in the risk and progression of AD. For example, specific gene variants in the VDR gene have been associated with an increased risk of developing AD [15].

The prevalence of AD is mainly revolving around genetic factors. Some of the genes found in the major histocompatibility complex (MHC) are responsible for elevating the susceptibility rate of AD. Human leukocyte antigen (HLA) genes have embroiled themselves in AD vulnerability [37]. In mid-stage AD patients, there is a slight elevation in the HLA-DR levels, but no change was seen in CD4, CD8, and IL-2 levels [58]. However, a considerable amount of change was seen in the moderate stage; due to the worsening of the condition, HLA-DR and CD4 increased, whereas CD8 declined. The statement mentioned above also informs us that we can observe that the immune reactions in AD are linked with the disease's clinical stage [34]. It has been reported that there is a visible increment in the MHC class II glycoprotein expression in the AD brain on its microglial cells and AD retinae [29].

It has been proven that HLA-DR alleles are correlated with Aβ T-cell epitopes, which is one of the major causes of AD progression. With continuous therapeutic immunization, we can observe a complete sweep of amyloid-β (Aβ) peptide from the parenchymal layer of the brain [6].

The neuroprotective effects of Vitamin D may be relevant to AD. It aids in lowering beta-amyloid plaque buildup, oxidative stress, and inflammation, which are all symptoms of AD [24]. Additionally, Vitamin D maintains calcium homeostasis and neuronal survival, both of which are essential for preserving memory and cognitive function [22]. Numerous aspects of brain health, including neurogenesis, synaptic plasticity, and the synthesis of neurotrophic factors, are known to be influenced by Vitamin D. These elements, which are crucial for the upkeep and operation of brain cells, are misregulated in Alzheimer's disease. Lack of Vitamin D may impede these procedures, causing the disease to manifest or worsen [53].

The immune system is influenced by Vitamin D, and chronic inflammation is thought to contribute to the pathophysiology of AD. Vitamin D has been demonstrated to control immunological responses and lessen neuroinflammation, which may be helpful in halting the progression of the disease [48]. Epigenetic modifications, which are adjustments to gene expression without affecting the underlying DNA sequence, have been linked to Vitamin D. Epigenetic modifications may alter how genes related to AD are regulated, thereby affecting the risk and course of the illness [18].

7.6 CORRELATION OF VITAMIN D LEVELS AND MMSE SCORE TO DETECT STAGES OF ALZHEIMER'S DISEASE

Serum 25-OHD levels and Mini-Mental State Examination (MMSE) test scores are related. Patients with sufficient vitamin D had significantly higher MMSE scores than those with low vitamin D levels (Table 7.1). MMSE score helps in segregating the different levels of AD [11].

TABLE 7.1 Correlation of Vitamin D and Symptoms Associated with Brain Disorders [54]

Stage	Range of Vitamin D	MMSE Score	Symptoms
MILD	Adequate (< 50 ng/mL->30 ng/mL)	26–18	• Difficulty in remembering recent activities • Loss of ability of maintain finance • Difficult in preparing food • May get lost while driving • Become lazy and may give up his hobbies

TABLE 7.1 *(Continued)*

Stage	Range of Vitamin D	MMSE Score	Symptoms
MODERATE	Insufficient levels (20–30 ng/mL)	17–10	• May require some assistance in performing daily task • Disorientation • May forget names of close ones • Agitation • Paranoid • Delusion • Hallucination • Poor hygiene
SEVERE	Deficient (<20 ng/mL)	9–0	• Loss of ability to speak • Cannot walk • Cannot feed himself • Insufficient voluntary control on urination and defecation. • Will require complete care

7.7 CLINICAL PRESENTATION OF ALZHEIMER'S DISEASE

In the early stages, the individual may experience lapses in memory and complain about difficulty recollecting the location of items or recalling what they had for breakfast. Both the affected person and those in their surroundings will observe these cognitive challenges in someone with Alzheimer's disease [20].

During the moderate phase of the illness, significant behavioral changes become evident in the patient. They may experience persistent feelings of sadness and irritability, and it is common for them to frequently forget names. As the disease progresses into the advanced stages, the patient's reliance on their caregiver for even basic daily activities increases significantly [19, 42].

7.8 THE ROLE OF VITAMIN D IN ASSISTING WITH THE MANAGEMENT OF AD

Alzheimer's disease management may benefit from the use of Vitamin D, according to some research. By lowering oxidative stress, inflammation, and the buildup of beta-amyloid plaques, it demonstrates neuroprotective

characteristics. Vitamin D may assist in normal brain function and slow down neurodegenerative processes by improving calcium homeostasis and regulating immunological responses. Better cognitive function and a lower risk of cognitive decline have been linked to adequate Vitamin D levels. Optimizing Vitamin D levels may show promise as an additional strategy for controlling AD, possibly slowing its progression and enhancing general cognitive function and quality of life, while further study is required to confirm its effectiveness and ideal application [59].

7.8.1 COGNITIVE FUNCTION

A lower risk of cognitive decline and greater cognitive performance has been linked to adequate Vitamin D levels. Optimizing Vitamin D levels in people with Alzheimer's may enhance cognitive function and decrease the illness's progression [52].

7.8.2 NEUROPROTECTIVE EFFECTS

In addition to lowering oxidative stress, inflammation, and the buildup of beta-amyloid plaques, which are hallmarks of AD, Vitamin D has neuroprotective qualities. Vitamin D may protect neurons and sustain brain health by reducing these harmful processes.

7.8.3 ANTI-INFLAMMATORY EFFECT

Alzheimer's disease progression is hypothesized to be influenced by chronic inflammation. With its ability to control inflammatory pathways and lessen neuroinflammation, Vitamin D has anti-inflammatory capabilities. Vitamin D may lessen some of the neurodegenerative processes linked to AD by reducing inflammation [10].

7.8.4 CALCIUM HOMEOSTASIS

Calcium homeostasis, which is essential for neuronal signaling and synaptic transmission, is maintained by Vitamin D. Disrupted calcium homeostasis is a factor in the malfunctioning of the neurons in AD. Calcium levels are

regulated by Vitamin D, which may maintain healthy neuronal activity and lessen the negative consequences of calcium dysregulation in the brain [25].

7.8.5 POTENTIAL EFFECT ON BETA-AMYLOID

One of the distinguishing characteristics of AD is the formation of beta-amyloid plaques from the aggregation of beta-amyloid proteins. According to recent studies, Vitamin D may affect the metabolism and removal of beta-amyloid, thereby preventing its buildup and boosting its removal from the brain.

7.8.6 MOOD REGULATION AND BEHAVIORAL SYMPTOMS

Depression and agitation, two behavioral symptoms that are frequently seen in Alzheimer's disease, have been linked to Vitamin D insufficiency. Enhancing Vitamin D levels may help Alzheimer's patients live better lives by lowering behavioral symptoms and improving mood [2].

Calcitriol, 1 alpha, 25-dihydroxy Vitamin D3 is considered to be the best active form of Vitamin D3 metabolites. It is the best suggestion for AD as its receptors are majorly present in CNS. It has been observed in many studies that daily oral Vitamin D supplementations for 12 months will show an immense improvement in cognitive functions and will also be responsible for decreasing the Aβ-related biomarkers in elderly patients with AD [31].

7.9 CONCLUSION

In this chapter, it has been discussed how Vitamin D and AD are related. Certainly, unequivocal evidence supports the positive role of Vitamin D in AD, as it effectively enhances cognitive performance in some AD patients. Genetic research has opened up the potential of identifying the proteins that connect vitamin D to AD pathogenesis. The pathogenesis of AD is also impacted by nongenomic mechanisms. Evaluation of vitamin D level is crucial in AD patients. Calcitriol is the most effective medication for AD because of its CNS receptor and active form of Vitamin D3 metabolite. The dose of calcitriol is modified using PTH and serum calcium levels. Since calcitriol inhibits the liver's ability to produce serum 25OHD, it is not required to check serum 25OHD levels following calcitriol administration.

PTH levels can rise and hypercalcemia can result from calcitriol. It is necessary to conduct more research on calcitriol and AD.

KEYWORDS

- **Alzheimer's disease**
- **calcitriol administration**
- **hypercalcemia**
- **neuroplasticity**
- **neuroprotection**
- **neurotransmission**
- **neurotrophy**
- **vitamin D**

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CHAPTER 8

Role of Non-Flavonoidal Agents in Alzheimer's Disease

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ABSTRACT

Among older individuals, Alzheimer's disease is the most prevalent cause of dementia, accounting for approximately 60% to 70% of all cases. As a neurodegenerative disorder, Alzheimer's has become a focal point in neuroscience research, aiming to understand the cellular changes and underlying mechanisms involved. Natural compounds, such as flavonoids, are believed to have the ability to cross the blood-brain barrier and have shown potential in the central nervous system. Consequently, these chemical components are being investigated for their effectiveness in slowing down the progression of neurodegenerative diseases. Diagnosis of Alzheimer's disease in dementia patients is based on the presence of neurofibrillary tangles and senile plaques, which are characteristic features of the condition. Although there are drugs like donepezil currently used to treat these ailments, they often come with adverse effects, leading healthcare professionals to explore alternative therapeutic options. While there is currently no definitive cure for Alzheimer's disease, pharmacological interventions are available to slow down its progression. Traditional herbal medicines used in many countries have been

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employed to prevent or treat neurodegenerative disorders and some have been formulated as nutraceuticals or dietary supplements. Non-flavonoid polyphenolic compounds are a specific category of natural compounds that have shown promise in the treatment of Alzheimer's disease. These compounds and their derivatives act as antioxidants, increase the expression of anti-inflammatory mediators, reduce Aβ aggregation and deposition of tau proteins, thereby protecting neurons and improving the condition of Alzheimer's disease. This chapter provides a brief overview of the pathology of Alzheimer's disease and explores the potential of non-flavonoid polyphenols and their derivatives as active agents against the disease.

8.1 INTRODUCTION

Neurodegeneration is a broad term that encompasses many disease conditions that impact different nervous system components either independently or in conjunction. Neurodegenerative diseases are commonly associated with disorders that affect a significant portion of the elderly population, with Alzheimer's disease (AD) being one of the most well-known and prevalent examples [1]. Alzheimer's disease is the main cause of dementia and one of the great health-care challenges of the 21st century [2]. It is defined by the gradual decrease of memory and cognitive functions, as well as changes in behavior and personality [3]. A German psychiatrist, Dr. Alois Alzheimer, in 1907, reported the first case of AD when he examined the brain of a woman who had died as a result of mental illness. He discovered a large number of aberrant aggregates, which are now known as amyloid plaques, as well as tangled bundles of fibers now called neurofibrillary or tau tangles [4]. An estimated 40 million people, mostly older than 60 years, have AD worldwide, and this figure is projected to double every 20 years [5]. The world prevalence of AD is assumed to increase to 1 in 85 people in 2050 [6].

Management of Alzheimer's disease is believed to be complex since no particular treatment has been developed to cure the condition. Currently available medications offer relatively small symptomatic benefit for some patients but do not slow disease progression [7]. Most AD therapies focus on managing neurological and behavioral issues that might worsen as the illness advances. The limited effectiveness, adverse effects, and poor patient compliance of modern therapy encourage the research of alternative AD treatments [8]. In the realm of drug discovery, natural products are regarded as a highly attractive alternative for treating Alzheimer's disease [9]. A

diverse range of classes of phytochemicals can be found in natural sources. The secondary metabolite polyphenols have garnered significant attention in drug development among the classes of metabolites. This is primarily due to their potential health benefits, which are largely attributed to their antioxidant properties, as noted by Sathya et al. in 2018 [10]. Polyphenolic compounds of natural origin demonstrate their antioxidant properties by either neutralizing free radical species or enhancing the endogenous antioxidant capacity, as reported by Choi et al. in 2012 [6]. In addition, certain compounds have been found to induce the production of intrinsic antioxidant molecules within cells by means of activating the Nrf/ARE pathway, as demonstrated by Dumont et al. in 2011 [11]. In addition to their antioxidant capacity, it has been observed that a majority of these compounds possess diverse molecular targets, affecting multiple signaling pathways and exhibiting pleiotropic effects on cells, as reported by Kim et al. in 2010 [12]. Polyphenolics have the ability to exert neuroprotective effects by modulating the activity of NF-κB or SIRT1. The efficacy of the FDA-approved treatments for Alzheimer's disease is not universal, as they do not possess curative properties nor do they impede the progression of the disease, and their therapeutic effects tend to diminish over time. This chapter will concentrate on non-flavonoid polyphenols and their subtypes in the management of Alzheimer's disease [13].

8.2 NON-FLAVONOID POLYPHENOLS

Polyphenolic compounds, consisting of multiple phenolic moieties, are commonly known as a diverse group of naturally occurring compounds. These compounds are abundant in fruits, vegetables, cereals, and beverages. They are widely acknowledged as the most common dietary antioxidants, with an estimated average intake of around 1 g/day per person. Synthetic polyphenolic compounds hold medicinal and industrial importance. Naturally occurring ring polyphenols have been found to possess a wide range of biological activities [14].

Polyphenols have the ability to interact with one-electron oxidants from a chemical perspective, thereby impeding the generation of free radicals in biological systems. The oxidation processes of single electrons are regarded as crucial stages of polyphenols when functioning as pharmaceuticals, as stated by Vermerris et al. in 2008 [15]. The bioactivity of these compounds holds significance due to their capability to interact with metal ions, such as Fe^{2+}, which can generate free radicals. Under certain conditions,

certain polyphenols may exhibit pro-oxidant properties [14]. Polyphenolic compounds can be categorized into two primary classes: non-flavonoids and flavonoids. Presently, the number of phenolic structures identified exceeds 8,000, with a subset of over 4,000 structures classified as flavonoids. Non-flavonoid polyphenols can be classified into various categories, including but not limited to phenolic acids, lignans, curcuminoids, anthraquinones, stilbenes, and xanthones.

8.2.1 PHENOLIC ACIDS

The phenolic compounds that are typically referred to as "phenolic acids" are those that contain one carboxylic acid group. Phenolic acids, also known as phenol carboxylic acids, are one of the primary categories of phenolic compounds found in plants. Polyphenols are a form of phytochemical. Seeds, the skins of fruits, and the leaves of vegetables have the greatest quantities of these phytonutrients, although they may be found in a wide range of plant-based meals. According to Pereira et al. in 2009 [16], it is uncommon for compounds to exist in their free form, as they are typically found in bound forms such as amides, esters, or glycosides. Phenolic acids are categorized into two main subgroups, namely hydroxybenzoic acid and hydroxycinnamic acid [17]. According to Tsao et al. in 2004, phenolic acids exhibit a significantly higher *in vitro* antioxidant activity compared to commonly recognized antioxidant vitamins [18]. Hydroxycinnamic acids are present in various food sources, frequently existing as uncomplicated esters conjugated with quinic acid or glucose. The aforementioned acids are produced through the process of cinnamic acid conversion. Chlorogenic acid is a predominant soluble bound hydroxycinnamic acid, which is primarily composed of caffeic and quinic acids. The four predominant types of hydroxycinnamic acids that are commonly detected are ferulic, caffeic, p-coumaric, and sinapic acids. Conversely, hydroxybenzoic acids are produced via the conversion of benzoic acid and possess a comparable structural composition, comprising a carbon chain spanning from C6 to C1. These entities can be present in a soluble state, wherein they are conjugated with sugars or organic acids, or they may be associated with cell wall constituents such as lignin [19, 20]. Hydroxybenzoic acids are frequently detected in red fruits, onions, and black radish, among other food sources, albeit in significantly lower quantities, in contrast to hydroxycinnamic acids. According to Shahidi et al. in 1995, the most commonly occurring types of hydroxybenzoic acid in nature are p-hydroxybenzoic acid, protocatechuic acid, vanillic acid, and syringic acid [21].

Phenolic acids possess neuroprotective properties through various mechanisms, such as reducing pro-oxidants and pro-inflammatory mediators, increasing the production and activity of antioxidants and anti-inflammatory mediators, enhancing the antioxidant machinery, promoting the release of neurotrophic factors, preventing protein aggregation, upregulating anti-apoptotic mediators, downregulating pro-apoptotic mediators, activating pro-survival signaling pathways while inhibiting cell death signaling pathways, and reducing the activity of reactive astrocytes and microglia [22].

8.2.1.1 CAFFEIC ACID

According to Basu et al. in 2016, current findings indicate that caffeic acid has the ability to exert neuroprotective properties by regulating neuroinflammation and oxidative stress [23]. A study was conducted to assess the efficacy of caffeic acid (CA) in inhibiting the aggregation of Aβ1–42 and disassembling fully formed fibrils in both a bulk solution and a membrane-like environment. For the purpose of this study, liposomes were employed as representative models of neuronal membranes *in vitro*. The compound CA demonstrated significant efficacy in suppressing the fibrillation process of Aβ1–42 in an aqueous environment, despite the presence of liposomes. Moreover, CA promptly disrupted preformed fibrils in the aqueous solution. The process of disaggregation undertaken by the CA was impeded by the existence of lipid membranes. The CA's process of disaggregation exhibited a gradual increase rather than an immediate one. The discernible dissimilarities in the disintegration patterns of fibrils could be attributed to the moderate affinity of CA towards the lipid bilayer. The study conducted by Andrade et al. in 2021 highlights the therapeutic efficacy of CA in both the prevention and treatment of AD [24].

8.2.1.2 FERULIC ACID (FA)

The neuroprotective efficacy of ferulic acid often relies on the synergistic interaction between its antioxidative and anti-inflammatory properties. According to Chen et al. in 2015, the administration of ferulic acid has been observed to increase the levels of serotonin and norepinephrine in the hippocampus and frontal cortex of mice, which are crucial brain regions involved in mood disorders [25]. However, dopamine levels were not found to be affected by ferulic acid. Ferulic acid, a compound consisting of a single

phenolic ring, is a metabolite of Curcuma. Research has demonstrated that curcuma exhibits neuroprotective properties, and these effects are attributed to ferulic acid's ability to modify the formation of Aβ fibrils, as well as its antioxidative and anti-inflammatory effects [26]. Due to the structural resemblance of FA to curcuma, it was hypothesized that FA may possess the capability to selectively bind to Aβ and impede the process of fibril formation. In addition, the condensed configuration of this structure may also be appropriate for targeted engagements with Aβ mature fibrils, potentially facilitating their subsequent destabilization, as suggested by Sgarbossa et al. in 2015. The utilization of FA has yielded favorable outcomes in hindering the neurotoxic Aβ-aggregation both *in vitro* and *in vivo* animal models. Moreover, FA has the capability to disrupt the biological pathways associated with apoptotic programmed cell death triggered by oxidative stress and inflammation resulting from Aβ aggregation, as reported by Sgarbossa et al. in 2015 [27].

8.2.1.3 GALLIC ACID

Gallic acid, a compound belonging to the trihydroxy benzoic acid class, is commonly present in plant metabolites and is widely distributed among various plant species. As stated by Gao et al. in 2019 [28], this substance possesses potent antioxidant properties and acts as a scavenger of free radicals, thereby providing protection against oxidative stress-induced damage to biological cells, tissues, and organs [28]. Gallic acid, a phenolic acid, exhibits antioxidant, anti-inflammatory, and neuroprotective properties, making it a promising candidate for the treatment of age-related cognitive decline and cognitive impairment resulting from illnesses. Extensive literature has documented these effects. The neuroprotective effects of gallic acid have been demonstrated in inhibiting NF-κB acetyltransferase, thereby mitigating the neurotoxicity induced by Aβ. Kim et al. in 2011 [29] found that gallic acid can reduce the production of cytokines by microglial cells. In a study by Kim et al. [29], gallic acid showed a counteractive effect against Aβ-induced cognitive impairment in mice [29]. Furthermore, another preclinical investigation revealed that the administration of gallic acid prevented memory impairments and synaptic deterioration by inhibiting the secretion of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α, consistent with the aforementioned findings [30].

8.2.1.4 SINAPIC ACID

Sinapic acid, also known as sinapinic acid, is a hydroxycinnamic acid naturally found in various plant materials of the Brassicaceae family. These include berries, oil seeds, vegetables like tronchuda cabbage, kale, white cabbage, turnip, cereals, and certain spices [31]. Research has demonstrated the neuroprotective effects of sinapic acid in various animal models of neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD). In a study conducted by Lee et al. in 2012, an AD mouse model was induced by injecting Aβ into the hippocampus. Oral administration of sinapic acid at a dosage of 10 mg/kg/day resulted in the rescue of neuronal cell death at the CA1 region and reduced the expression of iNOS, nitro tyrosine, and glial cell activation [32]. Another study showed that oral administration of sinapic acid at the same dosage prevented neuronal damage in mice challenged with kainic acid, particularly in the CA1 and CA3 hippocampal regions. This neuroprotective effect was accompanied by a decrease in reactive gliosis, iNOS expression, and nitro tyrosine formation in the hippocampus. Furthermore, sinapic acid exhibited anticonvulsant properties and enhanced memory function [33].

8.2.1.5 CHLOROGENIC ACID

Chlorogenic acid, specifically 5-O-caffeoylquinic acid, belongs to the hydroxycinnamic acid family and is categorized as a phenolic compound. Santana-Galvez et al. in 2017 [34] have documented the presence of chlorogenic acid in various food items and herbs, including but not limited to apples, carrots, artichoke, beetroot, burdock, coffee beans, eggplant, kiwi fruit, pears, plums, potatoes, tea, tobacco leaves, tomatoes, and wormwood [34]. The study by Mikami et al. in 2015 [35] demonstrated that chlorogenic acid (CGAs) can protect primary neurons from glutamate-induced neurotoxicity by regulating intracellular calcium concentrations [35]. The antioxidant properties of chlorogenic acids (CGAs) are associated with their ability to directly scavenge hydroxyl radicals, with efficacy depending on the dosage, as mentioned by Zhang et al. in 2003 [36]. Caffeoylquinic acids (CGAs) have been shown to alleviate oxidative stress and inhibit cellular apoptosis induced by various oxidative stressors and free radicals. This is achieved through the modulation of reactive oxygen species accumulation and the regulation of crucial proteins and enzymes involved in cell apoptosis. Due

to their high bioavailability in humans compared to other bioactive polyphenols, CGAs have the potential to produce beneficial effects in mitigating Alzheimer's disease (AD) [37].

8.2.1.6 P-COUMARIC ACID

p-Coumaric acid (p-CA), a phenolic acid compound, is naturally present in various vegetables, fruits, and cereals, including but not limited to potatoes, tomatoes, beans, onions, oranges, pears, apples, grapes, berries, maize, oats, and wheat. In recent years, p-CA has gained considerable attention due to its diverse range of biological and pharmacological properties. These properties encompass anti-inflammatory, antioxidant, anti-amyloidogenic, anti-apoptotic, anti-depressive, anxiolytic, and spatial cognitive-improving effects, as documented by Ghaderi et al. in 2022 [38]. The biosynthesis of this compound involves the conversion of tyrosine to p-CA through the catalytic activity of tyrosine ammonia-lyase. Subsequently, p-CA is transformed into various phenolic acids such as caffeic acid, ferulic acid, and sinapic acid, as well as other secondary metabolites including lignin and its precursors, feruloyl CoA, and p-coumaryl CoA [39]. Recent studies have shown that p-CA has the potential to enhance hippocampal neurogenesis and induce hippocampal synaptic plasticity [40, 41]. Furthermore, it has been observed that p-CA can protect against hippocampal long-term potentiation (LTP) impairment and cognitive decline induced by scopolamine. This effect may be attributed to its modulation of N-methyl-d-aspartate (NMDA) and α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, as well as its influence on central cholinergic synapses [42].

8.2.2 LIGNANS

Lignans are a group of secondary plant metabolites, as reported by Saleem et al. in 2005 [43]. They can be found in a diverse range of seeds, cereals, fruits, and vegetables. However, sesame and flax seeds are particularly rich in lignans, containing higher concentrations of this compound, as noted by Landete et al. in 2012 [44]. The amount of lignan intake and its subsequent bioavailability depend on the specific food consumed, and there can be significant variation among individuals, as discussed in studies by Touré et al. in 2010 [45] and Marcotullio et al. in 2018 [46]. Lignans are characterized as diphenolic compounds since they consist of two propyl-benzene units that

are chemically bonded together, as described by Pan et al. in 2009 [47], and they are synthesized through similar biosynthetic pathways, as studied by Suzuki et al. in 2007 [48]. Lignans can be further classified into eight structural subgroups based on the incorporation of oxygen and the pattern of cyclization, which include dibenzyl butyrolactol, dibenzo-cyclooctadiene, dibenzyl butyrolactone, dibenzyl butane, aryl naphthalene, aryl tetralin, furan, and furofuran, as identified by Solyomvary et al. in 2017 [49].

Lignans have demonstrated various beneficial biological effects, including anti-inflammatory, antioxidant, and anticancer activity, as reported by Ionkova et al. in 2011 [50]. Furthermore, some epidemiological studies have indicated a reduction in the incidence of cardiovascular disease associated with lignan consumption. However, the impact of lignans on other chronic illnesses, such as breast cancer, remains a topic of debate [51].

Recent pharmacological research has highlighted the potential of *S. chinensis* in preventing and treating age-related neurological conditions. The neuroprotective and cognitive-enhancing benefits of *S. chinensis* are primarily attributed to the presence of bioactive lignans in the plant. In the context of Alzheimer's disease, the lignans found in *S. chinensis* may mitigate the neurotoxic effects of neurological inflammation and oxidative stress. Additionally, they may help reduce the deposition of amyloid beta and the phosphorylation of tau by modulating various endogenous metabolic pathways [52].

8.2.3 CURCUMINOIDS

Curcuminoids, a family of active compounds found in turmeric, encompass polyphenolic pigments such as curcumin, dimethoxy-curcumin, and bisdemethoxycurcumin. While turmeric is known to contain a curcuminoid complex with medicinal properties, it constitutes only about 2.5%–6% of the rhizome. Among the curcuminoids, curcumin accounts for approximately 77% of the curcuminoid content [53]. The extraction of curcuminoids from the dried rhizome of Curcuma longa has been achieved using a batch extraction and three-phase partitioning (TPP) procedure [54]. Curcuminoids exhibit a yellowish-orange color and are insoluble in water and ether, but soluble in ethanol, dimethylsulfoxide, and other organic solvents [55].

According to a study, curcuminoids possess notable scavenging capabilities against various reactive oxygen species, including superoxide anion radicals and nitrogen dioxide radicals [56]. In addition, these

compounds have demonstrated inhibitory effects on lipid peroxidation in various animal models, as reported by Maheshwari and Singh in 2006 [56]. However, curcuminoids have also shown pro-oxidant properties in the presence of Cu^{2+}. Ahsan et al. in 1999 [57] found that the structural pattern of curcuminoids determines their antioxidant and pro-oxidant effects, implying that the efficacy of an antioxidant may vary across different systems and cannot be generalized [57]. The anti-inflammatory properties of curcumin are attributed to its ability to scavenge oxygen radicals. Curcumin has been observed to hinder the metabolic process of arachidonic acid and the activities of cyclooxygenase (COX) and lipoxygenase (LOX), while inhibiting the release of steroidal hormones. Its inhibition of the LOX enzyme leads to a reduction in pro-inflammatory leukotriene synthesis. Curcumin also exhibits significant inhibitory effects on pro-inflammatory cytokines [58].

Due to its pleiotropic effects and relatively low risk of side effects, curcumin is considered a promising substance for the treatment of Alzheimer's disease (AD) and related cognitive decline. Recent theories suggest that disruptions in various signaling pathways, particularly those regulated by inflammation and oxidative stress, may underlie these cognitive issues. As curcumin interacts with numerous molecules involved in these pathways, it holds potential as a compound for the prevention and treatment of cognitive decline [59]. Curcumin acts by reducing the formation of beta-amyloid plaques, preventing neuronal degeneration, chelating metals, reducing inflammation and oxidative stress, and inhibiting microglia production. The research explores the multiple mechanisms through which curcumin combats AD and its pathology [60].

8.2.4 ANTHRAQUINONES

Anthraquinones are a class of chemicals commonly found in the environment and categorized as quinones, benzoquinones, and naphthoquinones. They constitute a diverse group of approximately 700 different compounds, making them the most prevalent naturally occurring entities, as established by Duval et al. in 2016 [61] and Seigler et al. in 2012 [62]. Anthraquinones are ubiquitously present in various plant organs such as roots, rhizomes, fruits, and flowers. Additionally, they can be found in various food sources consumed by humans, including peas, cabbage, lettuce, and beans, among others, as reported by Diaz et al. in 2018 [63].

In addition to their common use as natural dyes, anthraquinones have been attributed with a range of biological activities in scientific literature, as discussed by Malik et al. in 2016 [64]. Notably, these compounds possess antitumor, anti-inflammatory, diuretic, antiarthritic, antifungal, antibacterial, antimalarial, and antioxidant properties [63, 65–68]. Some anthraquinones, such as physcion, chrysophanol, aloe-emodin, and rhein, exhibit a laxative effect, with physcion being particularly notable. This laxative effect is attributed to the presence of hydroxyl groups in the anthraquinone ring at positions C-1 and C-8 [69].

Abnormal aggregation of tau protein into paired helical filaments (PHFs) is a hallmark of Alzheimer's disease (AD). Anthraquinones have been found to inhibit tau aggregation and dissolve Alzheimer's PHFs *in vitro* and in cells, as demonstrated by Pickhardt et al. in 2005 [70]. Four rhubarb anthraquinones, namely emodin, CHR, rhein, and danthron, have shown therapeutic benefits in AD. In a study by Liu et al. in 2010 [71], emodin was found to significantly reduce cortical neuron mortality caused by Aβ25–35 and positively influence the expression of Bcl-2 and Akt phosphorylation while decreasing phospho-Jun-N-terminal kinases (JNK) ½ levels. Another study by Zeng et al. in 2018 [72] observed that emodin reduced Aβ levels and tau hyperphosphorylation in the hippocampal region of rats with AD-like symptoms, attributed to the downregulation of β-site amyloid precursor protein-cleaving enzyme 1 (BACE 1) levels and upregulation of protein phosphatase 2A (PP2A) activity [72]. CHR exhibited dose-dependent effects in enhancing neuronal cell survival and preventing apoptosis, as reported by Chae et al. in 2017 [73]. Rhein lysinate, studied by Liu et al. in 2013 [74], enhanced sirtuin 1 (SIRT1) expression and reduced β-amyloid precursor protein (APP) levels, leading to decreased TNF-α and IL-6, reduced ROS levels, and increased GSH-px and SOD levels in rats with an AD model [74]. Lastly, danthron demonstrated reduced membrane lipid peroxidation and inhibited Aβ-induced neuronal injury [75]. These studies collectively suggest the potential therapeutic use of anthraquinones in the treatment of AD.

8.2.5 STILBENES

Stilbenes are a group of plant secondary metabolites that originate from the phenylpropanoid pathway, as stated by Chong et al. in 2009 [76]. Phenolic compounds are derived from various plant families, including but

not limited to Vitaceae, Leguminaceae, Gnetaceae, and Dipterocarpaceae. Stilbenes are commonly found in various herbal and vegetable sources in the form of monomers, oligomers, and polymers, including viniferines, as reported by Teka et al. in 2022 [77]. According to Likhtenshtein et al. in 2000 [78], stilbene is a colorless compound that exhibits relatively low reactivity and is nearly insoluble in water [78]. Stilbenes are synthesized through biotic and abiotic stress responses, including microbial infections, elevated temperatures, and oxidative stress [77]. According to Langcake et al. in 1977 [79], the primary role of stilbenes in various plant families is to function as phytoalexins, which are defensive compounds produced in response to infection. Stilbenes exist in two isomeric states, namely trans-(E) and cis-(Z) configurations. The two isomeric forms of stilbenes exhibit distinguishable chemical properties and biological activity [79]. According to Morales et al. in 2000 [80], the introduction of hydroxyl groups into the primary structure of stilbene creates opportunities for the attachment of various substituents such as methyl and isoprenyl groups, sugars, and other residues. The formation of oligomeric stilbenes occurs through the process of oxidative coupling of both homogeneous and heterogeneous monomers, which are linked by either C–C or C–O–C units. The aforementioned procedure yields the synthesis of oligomeric stilbenes [80]. According to Ito et al. in 2012 [81], the trans-oriented aryl rings within the 1,2-diaryl-dihydrobenzofuran skeleton are considered to be the fundamental framework in stilbene oligomers of this category [81]. It is widely believed that this framework is synthesized through selective mechanisms that are both region-specific and stereoselective. Stilbenes have garnered significant attention due to their notable health-promoting attributes, including but not limited to anticancer, anti-inflammatory, anti-aging, antioxidant, and anti-atherogenic attributes [82, 83].

8.2.5.1 DERIVATIVES OF STILBENE IN TREATMENT OF ALZHEIMER'S DISEASE

8.2.5.1.1 Resveratrol

According to De et al. in 2017 [84], Resveratrol, a well-known stilbene compound, has been extensively studied due to its diverse range of biological properties. There has been speculation regarding its potential cardioprotective effects, attributed to its antioxidant properties, promotion of nitric oxide

production, inhibition of platelet aggregation, and potential to increase high-density lipoprotein cholesterol levels [84]. Resveratrol has also demonstrated anti-inflammatory, neuroprotective, and antiviral characteristics, as reported by Bhat et al. in 2001 [85]. Additionally, it is believed to possess neuroprotective properties, including the reduction of oxidative stress, inhibition of neuroinflammation, promotion of neurogenesis and micro-vessel formation, and facilitation of Aβ peptide clearance, as noted by Wang et al. in 2017 [86] (Figure 8.1).

Trans-resveratrol, also known as trans-3,4′,5-trihydroxystilbene, is a natural polyphenol predominantly found in red wine. Extensive research has focused on its potential health benefits, not only in Alzheimer's disease but also in conditions such as diabetes, obesity, and cancer, as mentioned by Freyssin et al. in 2020 [87]. Studies have shown that trans-resveratrol administration can reduce plaque deposits, particularly in the medial cortex, striatum, and hypothalamus, in transgenic animals expressing AD mutations [88]. In SAMP8 mice, a model of accelerated aging and sporadic AD, trans-resveratrol activated AMPK and pro-survival pathways, improved cognitive deficits, and reduced amyloid burden and tau hyperphosphorylation, indicating its neuroprotective effects against AD [89]. Additionally, in an AD rat model, trans-resveratrol improved spatial memory, reduced oxidative stress markers, and exhibited antioxidant effects [90].

Trans-E-viniferin, a trans-resveratrol dimer commonly found in grapevines and wine, has shown potential in mitigating memory impairment. Studies have found that its administration reduced amyloid deposition, astrogliosis, and microglial activation in a transgenic mouse model of Alzheimer's disease, suggesting a protective role for this polyphenol [91, 92].

Miyabenol C, a trans-resveratrol trimer extracted from the small-leaf grape Vitis thunbergii, has been studied for its effects on Alzheimer's disease. Treatment with miyabenol C led to a decrease in the levels of soluble β-fragment of amyloid precursor protein, as well as toxic Aβ42 and Aβ40, in the cortex and hippocampus, indicating its potential therapeutic benefits [93].

8.2.5.1.2 Piceatannol

Piceatannol, a derivative of trans-resveratrol, is commonly found in red wine, grapes, and white tea as a metabolite. It is also known as "astringenin" in academic circles. Hassaan et al. conducted an experimental study in

which they induced Alzheimer's disease (AD) in mice and administered piceatannol via intraperitoneal injection. The mice received a dosage of 2.5 mg/kg for 6 days, leading to improved cognitive function. Additionally, the concentration of Aβ42, a hallmark of AD, was significantly reduced in the brains of treated animals [87].

8.2.5.1.3 Pterostilbene

Pterostilbene is a naturally occurring stilbenoids compound with a similar chemical structure to resveratrol. It is initially extracted from sandalwood but is also found in fruits such as grapes and blueberries. Chang et al. in 2012 [95] found that pterostilbene intervention can reduce various markers associated with cellular stress, inflammation, and AD pathology, including manganese superoxide dismutase, peroxisome proliferator-activated receptor alpha, and phosphorylated tau [95]. In a study by Hou et al. in 2014 [96], pterostilbene was administered orally to mice before inducing cognitive impairment and neuronal alterations through intrahippocampal injection of LPS. The daily oral administration of pterostilbene at doses of 20 or 40 mg/kg resulted in improved cognitive function and a decrease in microglial cells and neuronal precursor cells in the hippocampus. These findings suggest that pterostilbene possesses anti-inflammatory and neuroprotective properties [96].

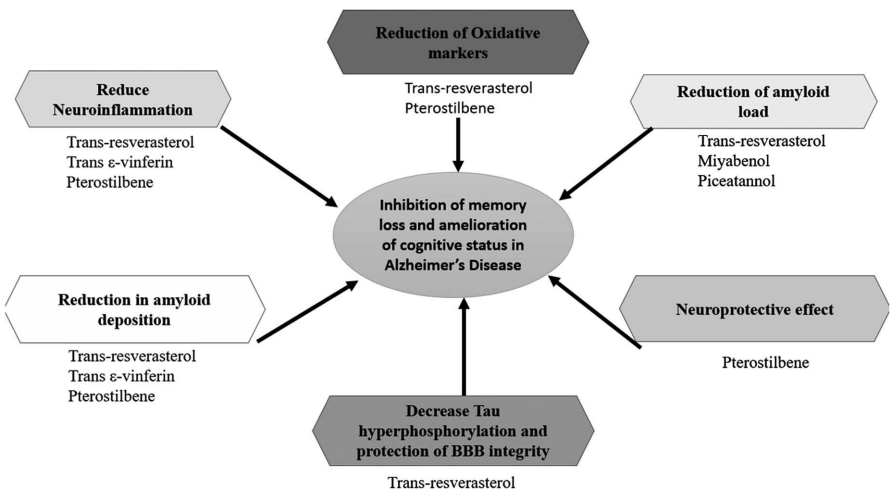

FIGURE 8.1 Role of derivatives of stilbenes in the treatment of Alzheimer's disease.

8.2.6 XANTHONES

Xanthones are a class of organic compounds that are present as secondary metabolites in a variety of terrestrial and marine flora, fungi, and lichen. Xanthones, which are also known as 9H-xanthen-9-ones, are a group of chemical compounds that possess a dibenzo-γ-pyrone heterocyclic scaffold containing oxygen, as stated by Resende et al. in 2020 [97]. To date, more than 250 xanthones have been isolated and identified in plant species belonging to the families Gentianaceae and Hypericaceae, as reported by Feng et al. in 2020 [98]. As per the proposition of Evans et al. in 1988 [99], the xanthone nucleus exhibits the potential to be acknowledged as a "privileged structure." This is due to its capacity to effectively bind to multiple distinct groups of protein receptors with a high degree of affinity [99]. The capacity of xanthones to disrupt a diverse range of biological targets is linked to certain distinctive molecular attributes. The characteristics of the compound in question encompass the existence of a heteroaromatic tricyclic ring system that is primarily planar and inflexible, a central ring carbonyl group that is proficient in multiple interactions, a biaryl ether group that augments the electronic system, and a xanthone core that can accommodate a diverse array of substituents at various positions, as reported by Pinto et al. in 2021 [100].

Several studies have demonstrated the significant biological properties of xanthones, including but not limited to antioxidant, anti-tumor, anti-inflammatory, and antiviral activities [101, 102]. In recent times, there has been a significant amount of research conducted on the chemotherapeutic properties of xanthones. This is primarily due to their ability to inhibit all stages of carcinogenesis. According to Sun et al. in 2002 [103], these compounds possess the ability to impede various molecular targets within the tumor cells, such as kinases, cyclooxygenases, ribonucleotide reductase, and DNA polymerases [103]. According to Shan et al. in 2011 [104], xanthones exhibit anti-tumor properties such as inducing cell cycle arrest, suppressing tumor cell proliferation, promoting apoptosis and differentiation, reducing inflammation, and inhibiting adhesion, invasion, and metastasis [104].

A group of xanthones has been extracted from the pericarps of Garcinia mangostana Linn, and have been identified as Mangostin, 8-Deoxygartanin, Gartanin, Garciniafuran, Garcinone C, Garcinone D, and c-Mangostin [105]. The majority of xanthones exhibited inhibitory effects on self-induced aggregation of β-amyloid (Aβ), β-site amyloid precursor protein-cleaving enzyme 1, and acted as antioxidants and

biometal chelators in both *in vitro* and *Escherichia coli* cellular contexts. The compounds α-Mangostin, Gartanin, Garcinone C, and c-Mangostin exhibited superior antioxidant properties in the elimination of Diphenyl-1-(2,4,6-trinitrophenyl) hydrazyl (DPPH) free radical when compared to Trolox. Additionally, these compounds demonstrated significant neuroprotective effects against glutamate-induced HT22 cell death, which can be attributed to the up-regulation of HO1 protein level and the scavenging of reactive oxygen species. According to Wang et al. in 2016 [106], it has been observed that Gartanin, Garcinone C, and c-Mangostin exhibit the ability to traverse the blood-brain barrier *in vitro* [106]. The administration of cholinesterase inhibitors is considered the most efficacious approach for treating Alzheimer's disease. This treatment strategy aims to prevent the hydrolysis of acetylcholine, thereby enhancing cholinergic postsynaptic transmission. Xanthones that occur naturally, such as those that are oxygenated, prenylated, pyrano, and glycosylated, have demonstrated significant potential in inhibiting acetylcholinesterase. The investigation into the structure-activity relationship of xanthones has demonstrated that the acetylcholinesterase inhibition activities are influenced by the type and position of the substituent(s) connected to the xanthone moiety. It has been observed that the presence of a hydrophobic moiety contributes to the π-π interactions, resulting in improved activity. Additionally, the hydroxy substituent(s) have been found to form hydrogen-bond interactions, further impacting the activity [94 107]. These results show that natural xanthones may be effective AD treatments due to their multifunctional effects.

8.3 CONCLUSION

As the incidence of Alzheimer's disease is continuing to grow globally, its management is getting difficult because there is no effective therapy that has been developed to cure the condition. The medications that are currently available offer a relatively small symptomatic benefit but do not completely cure the disease. The consumption of foods that are high in non-flavonoid polyphenols has the potential to slow the cognitive loss that is normally associated with aging, and it also has the potential to recover memory skills and slow the progression of disorders such as AD. Naturally occurring substances with numerous phenolic functions are collectively known as non-flavonoid polyphenolic compounds. They are

rich in medicinal properties and have fewer side effects compared to other allopathic drugs. These compounds have antioxidant, anti-inflammatory properties, and antiapoptotic properties. During AD, they prevent the aggregation of Aβ, hyperphosphorylation of tau protein, reduce the expression of antiapoptotic mediators, inhibit lipid peroxidation, etc. (Figure 8.2). All these properties help in the amelioration of AD. This chapter will provide a brief insight about the pathology of AD and the potential of non-flavonoid polyphenols and their derivatives as active agents against AD.

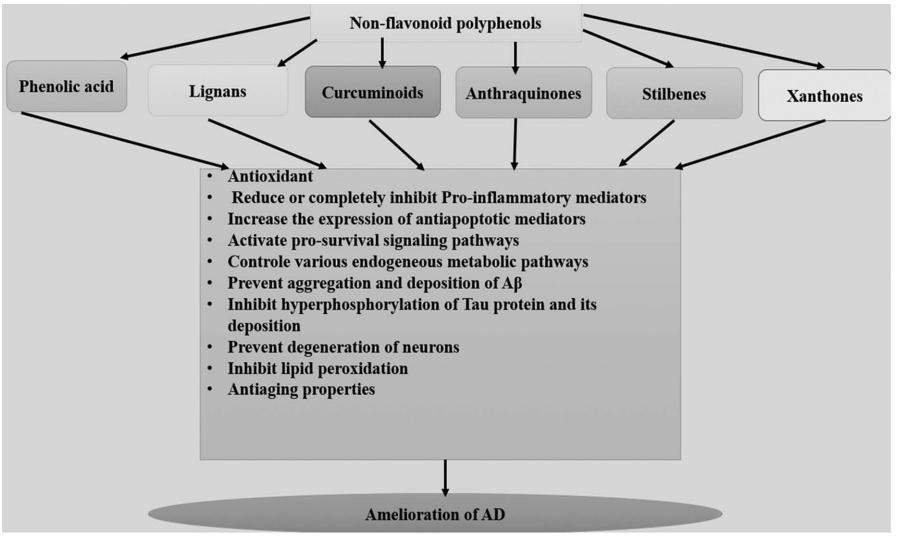

FIGURE 8.2 Various types of non-flavonoid polyphenols helping in the treatment of Alzheimer disease.

8.4 FUTURE PERSPECTIVES

This review provides a comprehensive analysis of numerous non-flavonoid compounds derived from various plant families that exhibit remarkable preclinical efficacy in combating Alzheimer's disease, along with an examination of their respective mechanisms of action. These types of analyses are recommended to be expanded towards the clinical and pharmaceutical investigations of non-flavonoid compounds. Therefore, it is imperative to develop innovative pharmaceutical formulations that utilize safe and cost-effective agents for the management of Alzheimer's disease in the future.

KEYWORDS

- **Alzheimer's disease**
- **amelioration**
- **cost-effective agents**
- **dementia**
- **good health**
- **herbal formulations**
- **pharmaceutical formulations**
- **polyphenols**

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PART II

Recent Developments and Advancements in Delivery of Nutraceutical Across the Blood-Brain Barrier

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CHAPTER 9

Drug Delivery Strategies for Drug Targeting to Alzheimer's Disease

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ABSTRACT

The Alzheimer's disease is a fatal neurodegenerative dementing disorder with earlier symptoms like mild cognitive impairment, that progresses remorselessly to a totally devastating complete loss of all cognitive functions. Science has come a long way from just discovering senile plaques (β-amyloid protein) and neurofibrillary tangles (tau protein) to understanding the major role they play in Alzheimer's disease. Demographic evidence suggests that 10–15% of people over 65 are affected, and the data increases to 47% of patients over 80, with an average survival time of 8 years after the first symptoms appear. Despite tremendous efforts to understand the disease's molecularity, the cure is still far away due to the lagging conventional therapy. Most drugs cannot cross the blood-brain barrier; even if they do, they cannot specifically target the affected brain regions. To tackle the challenge, numerous scientists have proposed advanced and innovative drug delivery strategies aimed at targeting drugs specifically for Alzheimer's disease using either nanotechnology or a smart drug delivery system. This chapter will present a holistic spread of all the strategies used in the current domain.

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9.1 INTRODUCTION

Alzheimer's is a fatal, progressive brain disorder that begins with mild memory impairment and progresses to dementia, affecting around 1.5 billion individuals worldwide, making it the 5th leading cause of death. This number is expected to increase fourfold by 2055. It mostly occurs in geriatric patients and poses an increased risk of impairment, liability, and financial loss, accounting for more than 1% of global GDP [1, 2]. Alzheimer's Disease (AD) is characterized by prolonged neuro-inflammation, where the gradual accumulation of amyloid beta (Aβ) or tau fibrils in the brain leads to the development of dystrophic neuronal cells. Despite intensive research efforts, developing efficient therapeutics for AD remains a significant challenge. One of the major obstacles in AD treatments is the targeted delivery of medications to the affected areas of the brain while minimizing systemic adverse effects. The blood-brain barrier (BBB) presents a complex and tightly regulated structure that often hinders traditional drug delivery strategies from achieving effective medication concentrations in the intended brain regions. Researchers are focusing on developing advanced medication delivery systems tailored for AD to address these challenges. These strategies aim to enhance medication bioavailability, treatment efficacy, and the delivery of therapeutic agents to the brain. To administer targeted medication delivery to the brain's afflicted areas, a number of strategies, including invasive and non-invasive methods, have been investigated. Utilizing surgical procedures such as intracerebroventricular or intraparenchymal administration, invasive techniques entail the direct introduction of medications into the brain. These techniques offer direct access to the target location, but they are also quite invasive and come with a lot of dangers, making them unsuitable for general clinical use. Because they provide safer and more palatable alternatives for patients, non-invasive medication delivery systems have attracted a lot of interest. These methods make use of a variety of mechanisms, including viral vectors, nanoparticles, liposomes, and exosomes, among others, to avoid or improve transport over the BBB. These carriers can encapsulate or conjugate medicines, preventing drug deterioration and enhancing medication penetration into the brain. Additionally, they can have their surfaces altered to improve BBB crossing and enable the administration of certain drugs to areas of the brain that are impacted by AD. Various drugs available which are approved by USFDA for AD are rivastigmine, donepezil, galantamine, and memantine. These drugs have been regarded as first-line treatment in AD, but they have their own side effects like nausea, vomiting, and diarrhea [3,

4]. Targeted drug delivery in AD is strenuous due to the Blood-Brain Barrier (BBB). To overcome this obstacle, various approaches are used. This chapter mainly focuses on how these approaches help to overcome this problem and deliver the drug to the target. It also focuses on how advanced nanoparticle strategies enhance the effect of CNS drug delivery in AD.

9.2 PATHOPHYSIOLOGY

Alzheimer's is a progressive neurological ailment defined by slow cognitive impairment, difficulties in executive function, communication, movement, and visual memory, and finally dementia [5]. The precise pathophysiology of AD is unknown. There are two key features of AD pathogenesis. Firstly, fragment aggregation or Aβ plaques are observed on the outer surface of neurons, and secondly tau tangles are seen in the cytoplasm of neurons. Several assumptions on the pathophysiology of AD have been reported, as discussed in Figure 9.1 [6, 7].

9.2.1 CHOLINERGIC DEFICIT

In AD, there is a significant decline in the number of cholinergic neurons in various hippocampal regions, nucleus basalis, and frontal cortex, which have a significant responsibility in terms of concentration, consciousness, and memory. These changes result in the dysregulation of cholinergic indicators such as acetyltransferase and acetylcholinesterase, which are indirectly linked to the onset of cognitive dysfunction in AD. There has been a broad understanding that the apparent association between cognitive deficits and reduced acetylcholine-mediated neurotransmission in the brain plays a crucial role in AD, but the exact cause of this illness is still unknown [8].

9.2.2 OXIDATIVE STRESS

Oxidative stress is a major contributing factor of AD. Its pathophysiology revolves around Reactive Oxygen Species (ROS) and its mechanism involves severe oxidative destruction of neuronal tissue in the brains of patients with AD. Cells create free ROS as a result of physiological metabolic processes or extrinsic pathophysiological stimuli such as radiation, poisons, and environmental contaminants. There are three major ways that promote the development of AD through oxidative stress [9, 10].

9.2.2.1 PEROXIDATION OF MACROMOLECULES

Peroxidation of macromolecules occurs when reactive oxygen species (ROS) oxidize lipids, proteins, and nucleic acids. Cellular malfunction and damage can result from peroxidation's damaging impact on cellular elements and functions. Peroxidation of macromolecules has been observed in the brains of individuals with Alzheimer's disease and is likely to be involved in the etiology of the condition.

9.2.2.2 DYSFUNCTION OF THE MITOCHONDRIAL AND REDOX REACTION OF METAL ION

As a consequence of oxidative phosphorylation in Alzheimer's disease, the malfunctioning mitochondria produce ROS. Oxidative stress results from an overabundance of ROS generation that overwhelms the cell's antioxidant defenses. In addition to causing cellular malfunction and the development of hazardous protein aggregates like beta-amyloid plaques and tau tangles, ROS can harm lipids, proteins, and nucleic acids. Alzheimer's disease is characterized by dysregulation of redox processes involving metal ions in addition to mitochondrial dysfunction. Copper, zinc, and iron metal ions all play significant roles in a number of physiological processes that occur within the brain. However, unfavorable interactions between these metal ions and beta-amyloid protein might cause redox processes that lead to the production of ROS. In Alzheimer's disease, the build-up of beta-amyloid plaques upsets the delicate balance of metal ion homeostasis, causing elevated metal ion levels and oxidative stress.

9.2.2.3 ROS PRODUCTION AND INCREASE THE PRODUCTION OF P-TAU AND AB

The increased synthesis and storage of beta-amyloid (Aβ) and phosphorylated tau (p-tau), two important pathogenic proteins, are intimately correlated with the generation of reactive oxygen species (ROS). Cellular oxidative stress can be caused by ROS, which are produced by a variety of processes, such as mitochondrial malfunction and dysregulated metal ion redox reactions, and can speed up the progression of Alzheimer's disease.

9.2.3 TAU PROTEIN HYPERPHOSPHORYLATED AND AMYLOID BETA

The production of senile plaques occurs because of amyloid beta aggregation, which is the most prominent characteristic seen in the patients of AD. The Aβ is a peptide obtained from the precursor of APP (amyloid precursor protein); these are usually seen in the brain of patients suffering from AD. Depending on the degree of oligomerization, there is a huge formation of Aβ, which results in several types of fibrils, toxic oligomer, and plaque formation. The cause to produce Aβ is yet unknown [11].

9.2.4 METAL IONS

The imbalance in the concentration of metal ions in the brain leads to the development of the disease. Inaccurate accumulation of iron, copper, zinc, or calcium in different regions of the brain causes overproduction of tau and amyloid beta. Iron, zinc, and calcium ions lead to the development of senile plaques and NFTs. AD patients have enhanced copper ion amounts that bind to amyloid beta and lead to the development of oligomers [12].

9.3 CHALLENGES IN DRUG DELIVERY

Physiological barriers and complexities of AD make the therapeutic delivery intervention a difficult task [13, 14]. The development of numerous medications has been rendered pointless, as they are unable to penetrate the blood-brain barrier. Consequently, in addition to exploring new entities and therapeutic candidates, researchers are also creating updated versions of current medications that target the brain [14]. Hence, understanding the challenges will help in designing intricate drug delivery systems that can diffuse deep into the CNS for better efficacy.

9.3.1 STRUCTURAL BARRIER OF BLOOD BRAIN BARRIER (BBB)

The central nervous system (CNS) requires a tightly controlled microenvironment to function normally. The brain is protected by different barriers. The BBB is a complex structure with different features situated between blood circulation and the central nervous system, which selectively prevent the movement of substances between them. Mainly two barriers are there to

control the movement of blood and nutrients through and across the CNS: Endothelial barriers – blood-brain barrier (BBB) located at every level of the cerebral vascular tree. Epithelial barrier – blood-cerebrospinal fluid (CSF) barrier located within the brain ventricular system at the choroid plexus, separating CSF and brain interstitial fluid (ISF) from peripheral blood flow of the brain. Both barriers closely regulate the movement of ions and biomolecules, allowing transport of oxygen and essential nutrients to the brain. The barriers help in the removal of toxins while protecting it from any potential injury that may exist in the periphery, creating and maintaining a highly well-regulated environment for optimal neuronal network [15]. In an average adult, the surface area of a BBB is estimated to be between 12 and 18 m^2, making it the biggest interface for blood-brain interaction [16–18].

BBB consists of endothelial cells which include pericytes and astrocytes as primary elements. Endothelial cells are connected through junctional proteins and encircled by the Basement Membrane which comprises nidogen, laminin, Type IV collagen, fibronectin, and perlecan. With the help of specific transporters, endothelial cells control the passage of ions, nutrients, plasma proteins, the movement of metabolites, and toxins. Pericytes, also known as mural cells, are becoming significant elements of the BBB due to their contractile capabilities, expression of receptors, transporters, release of signaling and inflammatory molecules. Pericytes are required for the formation of endothelial cell tight junctions; loss of pericytes may lead to altered efflux transport systems, altered BBB permeability, and increased endothelial transcytosis (transportation of macromolecules) and loss of tight junction proteins. They are becoming significant elements of the BBB due to their contractile capabilities, expression of receptors, transporters, release of signaling and inflammatory molecules. Astrocytes produce and secrete a wide variety of growth factors, proteins, peptides, neurotransmitters, chemokines, matrix proteins, cytokines, and lipid-transporting molecules which affect the activity of endothelial cells and pericytes [15].

There are certain substances, nutrients and drugs which can enter into CNS by means of one or more than one pathway, these pathways are meant to overcome the BBB restriction.

9.3.2 PASSIVE DIFFUSION

It's important to consider molecular weight when determining the free diffusion of small molecules, even if a compound has good lipid solubility. This

is because the permeability of the blood-brain barrier (BBB) is restricted for compounds with a molecular weight over 400 Daltons. This is due to the fixed size of the BBB pores, which restricts the movement of molecules with a spherical volume greater than the pore volume. It's a common misconception that small molecules can easily pass through the BBB, but in reality, more than 98% of all small compounds are unable to do so. Despite the Comprehensive Medicinal Chemistry (CMC) database containing over 7,000 medicines, only 5% of them are used to treat neurodegenerative disorders [19].

9.3.3 ACTIVE EFFLUX

ATP-binding cassette (ABC) proteins expressed by the BBB's luminal endothelial plasma membrane are responsible for the active transport of various substances across the blood-brain barrier. They are ATP-derived efflux pumps which are used to restrict the permeability of a variety of toxins, endogenous metabolites, and drugs. It has been shown that patients with various neurological disorders have lowered ABC transporter expression and functional activity. Breast cancer resistance protein, Multidrug resistance-associated Proteins (MRPs, ABCC1, 2, 4, 5, and possibly 3 and 6), and P-glycoprotein (P-gp) are the important efflux transporters at the BBB [19]. It was evident from the literature that Aβ peptide accumulates in the brain when ABC transporters in an AD animal model are affected. P-gp has been widely studied among these transporters due to its contribution to Aβ efflux from the brain parenchyma. Different mouse model studies have found that a P-gp deficit leads to the deposition of Aβ and pronounced sensitivity to several drugs. Multiple studies conducted on tissue samples from cadaver brains (post mortem of AD patients) have consistently found lower levels of P-gp and ABC efflux pumps. Human P-gp has a molecular weight of 170 kD and 1,280 amino acids. It belongs to the ATP-binding cassette transporter superfamily of transporters. Most P-gp substrates in the BBB are a heterogeneous mix that includes medicines and poisons as well as other endogenous substrates such as amyloid beta protein and gangliosides GM1. In Alzheimer's disease, P-gp function is reduced because of neuroinflammatory conditions in the brain. In the previous section on active efflux, it has already been discussed that due to the disruption of P-gp activity, amyloid β cannot efflux completely and thus accumulates to form Aβ plaques. Since several commonly used medicines are P-gp substrates, a decline in P-gp

activity might have many implications for the use of CNS medications in AD. Tumor necrosis factor-alpha, on the other hand, can boost P-gp activity and hence reduce drug access to the brain. It is possible that increased availability of these drugs in the brain, or sudden restriction of drug transport into the brain, leads to increased sensitivity of AD patients to the onset of delirium [17, 20].

9.3.4 BBB DYSFUNCTION IN AD

Many neurological illnesses, including Alzheimer's and Parkinson's, disturb the BBB. Inflammation has been associated with BBB abnormalities in various disorders. Disruption in BBB leads to progression of AD. Libener et al. explained that expression of glucose transporter (GLUT1) gets lowered in capillaries of the brain as illustrated in an animal model of AD. Moreover, GLUT1 deficiency leads to the loss of TJ proteins and BBB disruption. In Alzheimer's, the brain endothelial cells' level of low-density lipoprotein receptor protein 1 (LRP1) gets reduced, which basically facilitates the outflow of Aβ from the brain. The expression of the Receptor for Advanced Glycation End Products (RAGE) is increased, which ultimately leads to an increase in the influx of Aβ inside the CNS and accumulation of Aβ in the brain. In AD, Aβ contributes the most to BBB disruption as Aβ accumulation in the brain also leads to increased BBB permeability. Tau protein also affects the structural activity of the BBB; hence, both Aβ and tau lead to dysfunction of the BBB.

9.3.5 CARRIER MEDIATED TRANSPORT (CMT)

Carrier-mediated transport by means of solute carrier transporters involves the movement of molecules across a cell membrane with the help of specific carrier proteins [21]. Some of the solute carrier transporters involved in inflow at BBB include Glut-1 and Glut3 for glucose and mannose hexose transport system, a neutral amino acid transporter for the transport of neutral amino acids, and transporters like LAT1 and LAT2 for drugs like levodopa [22].

9.3.6 RECEPTOR-MEDIATED TRANSPORT (RMT)

Bulky proteins are unable to pass the BBB even when utilizing amino acid CMT systems. However, hormones, regulatory proteins, growth factors, and

specific neuroactive peptides use RMT systems to pass through the BBB. Large molecular weight solutes use endocytosis mechanisms to enter the CNS; this entire mechanism is known as transcytosis. RMT occurs when a receptor binds to a macromolecule specific to a ligand on the cell surface, resulting in an endocytotic event [23].

9.4 TREATMENT APPROACHES

9.4.1 CONVENTIONAL APPROACHES

Up until now, there are 5 drugs that have been approved by the FDA for clinical use in treating the symptomatic manifestation of Alzheimer's disease (AD). These drugs fall into two categories: acetylcholinesterase inhibitors (AChEs), which include donepezil, rivastigmine, galantamine, and tacrine, and non-competitive NMDA receptor antagonists, which include memantine. These drugs are considered first-line treatments for mild to moderate AD. All of these drugs aim to counterbalance the disruption of neurotransmitters caused by the disease, and they only serve to slow down the onset of AD symptoms. Recent developments in nanotechnology provide a unique opportunity to improve the prevention, early detection, and treatment of AD and to address the limitations of traditional pharmacological therapy. However, the effectiveness of these drugs can be influenced by properties such as lipophilicity, stability, and molecular weight, which restrict the passage of drugs to the brain. Hence, we need another way for entering the BBB. For the same intranasal drug delivery, BBB disruption techniques, prodrug were most commonly used strategies (Figure 9.1) [24, 25].

9.4.2 INTRANASAL DRUG DELIVERY (SOLUTIONS, SUSPENSIONS, AND EMULSIONS)

For the direct and practical administration of AD medications, the intranasal route is available. In the intranasal route of administration, the drugs are first incorporated into the nasal epithelium and then delivered to the brain. These drugs will be supplied by the extracellular pathway, which is one of the quickest methods for compounds to reach the CNS. So, with this method, it is not necessary for the drug to bind to transcytosis receptors in order to be effective. A detailed evaluation of the brain distribution pattern is required for successfully developing an intranasal drug delivery carrier, with a focus

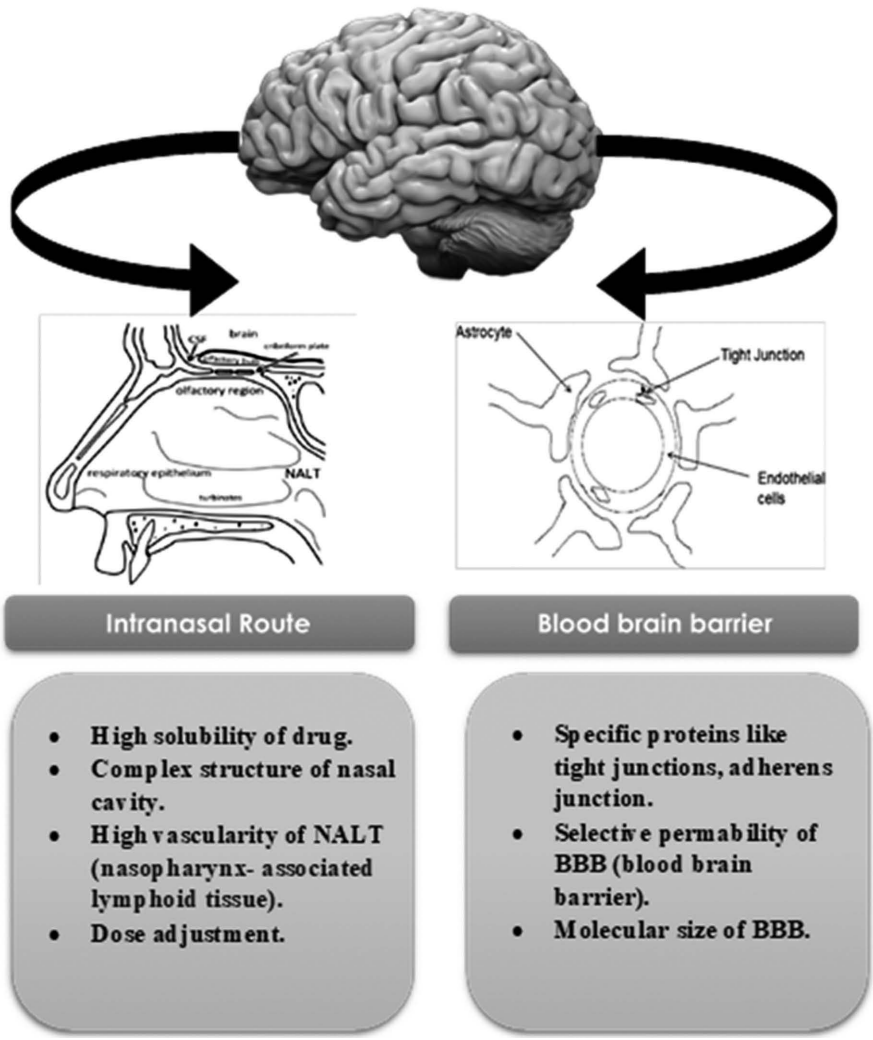

FIGURE 9.1 Illustrating two strategies practiced for effective brain delivery.

on the drug exchange between the parenchyma and CSF. Each medicine has a specific target site in the brain; therefore, a clear understanding of the disease pathogenesis and target variables is vital for creating an efficient drug delivery [14]. In adults, the nasal cavity has an incredibly huge surface area of about 160 cm^2. It is typically split horizontally by the nasal septum and stretches around 12–14 cm from the nostrils to the nasopharynx; these two parts are divided again into three domains: 1. The Nasal Canal, 2. The

Pulmonary Area, and 3. The Olfactory region [26, 27]. Nasal-associated lymphoid tissue is also found in the nasal cavity, mostly in the nasopharynx, which is located at the back of the nasal cavity. NALT is a form of mucosal-associated lymphoid tissue that eventually leads to lymph nodes. Thus, because of lymphoid tissue, drugs will be directly delivered [28]. Since the dosage is restricted to 20–30 µl, administering larger amounts requires compounds that have higher solubility. The drug formulation's pH and solubility both impact the delivery of drugs. Mucociliary clearance of the nasal route is also a limiting factor to consider before designing intranasal drug delivery systems. Additionally, intranasal delivery necessitates deft maneuvers since incorrect injection may result in the drug being delivered to the lung or stomach [29, 30].

Conventional routes like oral and intravenous have some drawbacks related to the inability to cross major physiological barriers, i.e., gastric barrier, BBB barrier, etc. Therefore, to overcome these limitations, researchers find refuge in intranasal routes as a substitute for oral delivery. There are multiple physiological features that are advantageous for brain delivery in the case of intranasal delivery. The large surface area of nasal mucosa and profuse vascularization underneath help for better drug absorption. Other advantages include circumvention of first-pass metabolism, bypassing the harsh gastric GIT environment, and a non-invasive technique for compliant patients. The effectiveness of the intranasal route is influenced by the exact composition, physical characteristics of the drug, and the kind of nanocarrier used [25, 31]. Shi et al. conducted a study on 5XFAD mice and Wild type (WT) B6SJLF1/J mice where they compared the subcutaneous and intranasal administration of dantrolene and observed that treatment with dantrolene massively reduced impaired memory [32]. Although intranasal delivery has its own challenges, which will be discussed in later sections.

9.4.3 BBB DISRUPTION TECHNIQUES

Many methods are being investigated in the field of Alzheimer's research to circumvent or disrupt the blood-brain barrier (BBB) and improve medication delivery to the brain. These strategies try to get around the problem of poor medication penetration into the brain, which is a major barrier to creating effective Alzheimer's disease therapies. It is another approach for the treatment of AD in which molecules are allowed to enter or cross the BBB, which might lead to the opening of the BBB. It is an invasive technique; hence it

comes with many consequences as well. Several techniques of the disruption of BBB are focused ultrasound, laser-based thermotherapy, osmotic pressure, and iontophoresis. The most widely used methods are focused ultrasound and the opening of BBB by osmotic pressure [33].

9.4.3.1 FOCUSED ULTRASOUND

Focused ultrasound (FUS) with microbubble-mediated transient BBB opening has gained interest due to its growing therapeutic drug delivery to the brain. The BBB itself has an anti-amyloid effect. Several preclinical drug studies have emphasized the use of FUS to penetrate the BBB, thus helping in lowering phosphorylated tau and Aβ load, resulting in improved cognitive performance. Previous literature demonstrates the existence of two human studies conducted on BBB opening in Alzheimer's: Lipsman et al. conducted a phase 1 study which mainly targeted the right frontal lobe and observed that after opening the BBB, Aβ levels decreased. A phase 2 study was done by Rezai et al. targeting the hippocampus and entorhinal cortex. However, none of these trials showed significant cognitive impairment [34].

9.4.3.2 OPENING OF BBB BY OSMOTIC PRESSURE

In recent years, scientists have investigated a number of methods to momentarily break through the blood-brain barrier, improving medicine delivery to the brain. One such strategy includes breaking up the blood-brain barrier's tight connections between the cells using osmotic pressure.

Osmotic pressure is a real phenomenon that occurs when a semipermeable membrane experiences a change in solute concentration. It is possible to temporarily increase the permeability of the blood-brain barrier by creating a hyperosmotic environment in the blood vessels surrounding the brain. A hyperosmotic substance, such as mannitol, is commonly administered intravenously when utilizing the osmotic pressure technique. Due to its osmotic properties, mannitol, a sugar alcohol that is not metabolized by the body, can draw water through the blood-brain barrier. By injecting mannitol into the carotid artery using this method, large molecules can enter the central nervous system. This occurs because when the endothelial cells of the blood-brain barrier come into contact with mannitol, they shrink, opening the paracellular pathways and allowing molecules to enter the CNS. Patients who have undergone this treatment have shown increased life expectancy

and no significant adverse effects. Therapeutic drugs that would typically not cross the blood-brain barrier can be delivered once the barrier is temporarily opened. This approach has the potential to enhance the delivery of medications targeting tau tangles, beta-amyloid plaques, or other pathological processes associated with Alzheimer's disease. While the osmotic pressure technique seems promising for improving drug delivery in Alzheimer's, it is still in the early stages. The main concern with this treatment is that long-term effects cannot be predicted; a few cases of seizures have been reported [33].

9.4.4 PRODRUG APPROACH

Poor physicochemical properties of the drugs limit the widespread usage of the drugs. Levodopa is a prominent prodrug of dopamine, designed to provide easy access to the brain by passing the BBB. To give a pharmacological effect, prodrugs need to convert into the active form by undergoing enzymatic or chemical metabolism. Over the past decades, the FDA has allowed many prodrug approaches for various diseases and disorder treatments. The development of prodrugs is anticipated to take the limelight in the upcoming years. Prodrugs are classified into different categories such as pleiotropic, ester/amide, thiol-based, bio-oxidizable, Mannich, peptide-based prodrugs including drugs like naproxen, serotonin, ferulic acid, perforin [35]. Sestito et al. fruitfully formulated memit from memantine by replacing the free amine group of memantine with an isothiocyanate activity and observed pharmacological activity *in vitro*. It showed that memit inhibited Aβ self-aggregation and displayed cytoprotective effects against Aβ oligomers induced destruction of rat microglial cells and human brain. It is also observed that memit, like memantine, induces autophagy and survival, both of which are impaired in Alzheimer's disease. As a result, it is apparent that memit is a prodrug of memantine [36].

9.4.5 MISCELLANEOUS

Various traditional methods of intranasal drug delivery, such as nasal sprays, nasal gels, nasal powders, and nasal drops, are commonly utilized to treat a range of diseases and are developed for both topical and systemic administration.

9.4.5.1 NASAL POWDERS

Nasal powders have become an attractive option for drug delivery due to their higher drug stability compared to solutions or suspensions and the absence of preservatives. Fasiolo et al. conducted a study in which they developed nasal powder containing flurbiprofen and evaluated it *in vitro* and *in vivo* for early treatment of AD. Flurbiprofen is a nonsteroidal anti-inflammatory drug (NSAID). Long-term oral NSAID use in rheumatoid arthritis patients has been found in epidemiological studies to reduce the likelihood and prevent the onset of AD [37]. Quercetin is a flavonoid with promising therapeutic properties for the treatment of Alzheimer's in its initial phases, but there are certain limitations like prolonged first-pass response and poor solubility which make it incompatible for oral delivery. Papakyriakopoulou et al. conducted a study in which they developed a combination of nasal powders containing quercetin-cyclodextrin to improve the delivery of quercetin into the brain. *In vitro* results of the powder showed quick solubility and penetration 17 to 48 times greater than pure quercetin [38].

Nasal powders are not commonly used in intranasal delivery studies due to their limitations in particle size, solubility, and aerodynamic characteristics [37].

9.4.5.2 NASAL GEL

Nasal gels are highly viscous in nature, which prevents them from leaking after application, reduces discomfort from the formulation's lubricating additives, and more effectively targets the mucosal membrane for greater absorption. Qian et al. conducted a study in which they developed an in situ gel formulation containing tacrine. The ability of a formulation to be delivered in a liquid state at temperatures below 20°C and to solidify at the delivery site at 28.5°C is referred to as "in situ gel." Results showed that compared to an oral solution of tacrine, the in situ gel demonstrated greater absorption in the nasal cavity of rats [37]. Espinoza et al. conducted a study in which they developed three different intranasal gels of donepezil using chitosan and pluronic. To differentiate between the three distinct gels, their rheological properties, pH, geling temperatures, morphology, and swelling characteristics were all examined. Findings demonstrated that pluronic gels showed better results compared to chitosan gel in terms of release rate and penetration. Therefore, the administration of nasal gels may be a potential way to increase donepezil's permeability [39].

9.5 ADVANCED TARGETING APPROACHES

Since its discovery, Aβ plaques are regarded as the earliest event in the AD process. However, no treatments have been discovered so far to cease the accumulations of cognitive and functional dysfunction. However, there are a few drugs that can help reduce the progression by slowing down the accumulation of the Aβ plaques. The failure of previous experiments has prompted researchers to look at new therapy options. Some of the novel treatment approaches are as in subsections.

9.5.1 AMYLOID CASCADE TARGETS

According to the amyloid cascade theory, accumulation of Aβ plaques leads to neurodegeneration in AD. Aβ plaques act as a pathogenic catalyst for a chain of events that result in cell death, neurotic damage, and the development of neurofibrillary tangles from tau protein. From a treatment and diagnostic perspective, Aβ binding compounds have been conjugated to NPs due to their lack of toxicity, minimal immunogenicity, and complete biodegradability. Liposomes and PEG-PLA (polyethylene glycol–polylactic acid) nanoparticles (NPs) may be the most often used NPs. Mourtas et al. found that curcumin derivative-conjugated liposomes had a high affinity (1–5 nM) for Aβ fibrils in *in-vitro* studies. Pederzoli et al. investigated the potential application of nanomedicine to overcome the KLVFF limit of distribution. KLVFF is a peptide that interferes with Aβ aggregation. They produced new polymeric nanoparticles (NPs), evaluated the effectiveness and toxicity findings, and demonstrated the effective creation of KVLFF-loaded NPs, which were significantly more effective in reversing Aβ-induced diseases than the free peptide without having a discernible impact on cell health. DBP (vitamin D binding protein) can reduce the build-up and aggregation of Aβ. Jeon et al. investigated that DBT can be put into a biocompatible polymer called poly(D, L-lactic acid-co-glycolic acid) (PLGA). NP-PLGA NPs therapeutic effects in Aβ overexpressing (5XFAD) mice were investigated using a PLGA-based drug delivery system. They discovered that Aβ aggregation *in vitro* was considerably reduced by DBP-PLGA NPs. Additionally, they also discovered that DBP-PLGA NPs intravenous administration dramatically reduced Aβ build-up, neuroinflammation, neuronal death, and cognitive impairment in the 5XFAD animals [28, 35, 40, 41].

9.5.2 TAU PROTEIN AGGREGATION BLOCKER

Neurofibrillary tangles and phosphorylation of tau protein also lead to the progression of AD. Several studies have been conducted on amyloid-targeted drugs, but none have been able to demonstrate constructive and progressive results. Therefore, researchers are now forced to discover agents that help inhibit the accumulation of tau as well as the degeneration of tau, such as aminothienopyridazines, curcumin derivatives, methylene blue, N744, and rhodamines. Wischik et al. conducted a study and observed that methylene blue can suppress or remove tau aggregation. Curcumin is also found to be effective in controlling the progression of AD. Despite curcumin's medicinal properties, its low solubility, stability, and bioavailability make it unsuitable for clinical application. Okuda et al. conducted research resulting in the discovery of the new curcumin derivative PE859 (3-[(1E)-2-(1H-indol-6-yl) ethenyl]). It is a selective tau inhibitor and Aβ accumulation with suitable pharmacological properties. According to a study conducted by Feng et al., a non-flavonoid polyphenolic substance called resveratrol, prominent in red wine, suppressed the Aβ fibrillary level in cell lines and APP/PS-1 transgenic mice [28, 42–44].

9.6 ADVANCED NANOPARTICULATE-BASED DRUG DELIVERY STRATEGIES

AD is a brain disorder which causes loss of neurons and ultimately leads to death of cells. The major challenge faced in AD is delivering the drug into the brain, and this is because the BBB has poor permeability. To overcome this disease, many approaches have been attempted. Nanotechnology has certainly emerged as a major player in bringing newer advanced drug delivery systems (Figure 9.2). Nowadays, nanotechnology has been widely used for the treatment of neurodegenerative diseases using a strategy-controlled drug delivery system in the brain. This delivery method makes use of a wide range of nanoscale drug delivery platforms, primarily lipid- and polymer-based nanoparticles (NPs), which guarantee a controlled and enhanced release of the drug by preventing loaded pharmaceuticals from being digested [45]. The physicochemical characteristics and precise targeting of NPs are both essential for their therapeutic uses. Surface charge, in addition to form, size, and functionalization, plays a significant role in NP cellular uptake and barrier permeability as their primary focus is enhancing NPs' capacity to accurately target the therapeutic site [45–47].

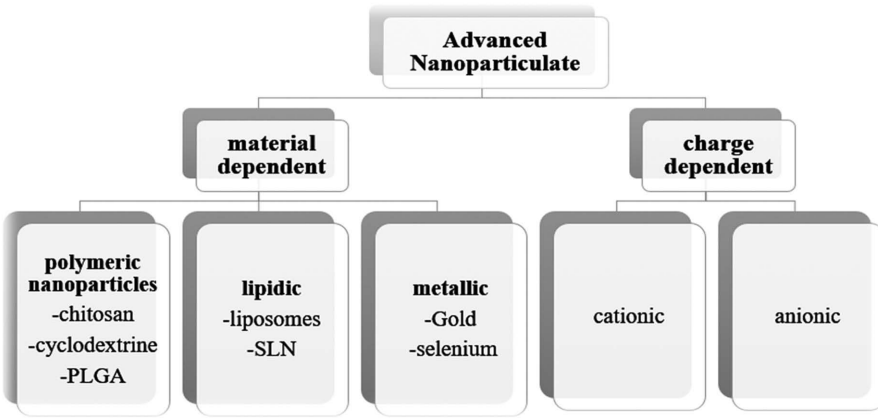

FIGURE 9.2 Flowchart showing classification of advanced nanoparticulate based drug delivery strategies.

9.6.1 MATERIAL DEPENDENT

AD is a brain disorder causing neuron loss and cell death. A major challenge in AD is delivering drugs to the brain due to poor BBB permeability. Various approaches have been tried to overcome this disease. Nanotechnology plays a key role in advanced drug delivery systems. Nanoparticles are used as carriers made from organic and inorganic materials for targeted medication delivery. Material specific texture, functional groups, hydrophilic and hydrophobic properties influence the interaction with BBB [47, 48]. In the next sections we have provided different materials from which various NPs were prepared and tested for their BBB penetration.

9.6.1.1 POLYMERIC NANOPARTICLES

9.6.1.1.1 Chitosan Nanoparticles

Chitosan comes under the category of natural polymers. It is a biocompatible polymer often used as a material in drug delivery systems for brain disorders. Derivatives of chitosan have a biological effect on the BBB and neuronal cells that are helpful in the treatment of AD. Upon hydrolysis, it converts into a non-toxic, non-carcinogenic amine sugar product. This product is easily absorbed and degraded by the body; therefore, chitosan is considered a biodegradable polymer. Chitosan for biomedical purposes is used in wound healing and is approved by the FDA for the same [47]. Elnaggar et

al. demonstrated a study to evaluate the activity of piperidine filled with chitosan NPs on an animal model of senile dementia of A type (SDAT). This model is used to study the cognitive impairment caused by colchicine. The researchers found that all decreased levels of Ach were restored by piperidine-loaded chitosan NPs. The NPs were able to produce a strong response with very high anti-AD potency [4, 49]. Galantamine hydrobromide (GH) was found to be a drug that reduces the formation of plaques in 5XFAD mice; it is an inhibitor of AchE. During human trials, GH showed adverse effects upon oral administration, so researchers need another drug delivery system to deliver GH to the brain to reduce its adverse effects. Hanafy et al. developed a complex of GH and chitosan nanoparticles through a reaction between them. They conducted a study in which the pharmacological and toxicological effects of GH-chitosan complex nanoparticles and free GH were compared. The study was conducted on the brains of rats through intranasal administration, and it was found that compared to free GH, the GH-chitosan complex nanoparticles substantially decreased the brain AchE levels [50].

9.6.1.1.2 Cyclodextrine

Cyclodextrins (CDs) are a type of cyclic oligosaccharides that possess a unique supramolecular structure resembling a cage. The internal cavity of the CD has the ability to accommodate lipophilic molecules and form stable, water-soluble complexes with them, without forming covalent bonds. By using CD inclusion complexes as drug delivery systems (DDSs), the solubility, bioavailability, and stability of the drug payload can be significantly enhanced [29]. Yao et al. investigated the hydroxypropyl-β-CD (HP-β-CD) in cell and mouse models of AD. It was found that CDs exhibited neuroprotective properties in both cell and transgenic mouse models of Alzheimer's disease by reducing the production of Aβ and improving its clearance mechanisms [51].

Wong et al. conducted a study in which they developed a CRT-γ cyclodextrin inclusion complex (CRT–crocetin). The water solubility and bioavailability issues associated with Crocetin (CRT) have hindered its development as a therapeutic candidate for Alzheimer's disease (AD), despite its potential neuroprotective effects. Pharmacokinetic and biodistribution studies showed that the CRT-γ-cyclodextrin inclusion complex significantly increased the bioavailability of CRT and facilitated its crossing of the blood-brain barrier to

enter the brain. These findings indicate that the water-soluble γ-cyclodextrin inclusion complex can effectively deliver CRT across the blood-brain barrier. Furthermore, compared to the CRT-free medication, it showed a stronger ability to suppress the expression of C-terminus fragments and the amount of amyloid in the 7PA2 cell line [52].

9.6.1.1.3 PLGA

The FDA has authorized the polymer poly(lactide-co-glycolide) acid (PLGA), which is a highly utilized polymer in the pharmaceutical industry due to its desirable properties such as biodegradability, biocompatibility, capacity for mucoadhesion, controlled drug release, and versatility in encapsulating diverse drug types, making it an excellent material for creating drug carriers. Seju et al. conducted a study to evaluate the potential of using PLGA nanoparticles to improve the bioavailability and brain targeting of olanzapine. Olanzapine is an antipsychotic drug. They synthesized the nanoparticles using a nanoprecipitation method. The drug was released from PLGA nanoparticles by 59% according to the *ex vivo* results after about 3 hours. Studies conducted *in vivo* rat model showed a significant increase in the drug's uptake in the brain when administered intranasally, compared to the drug used alone. PLGA nanoparticles (NPs) with an average particle size of less than 300 nm were prepared using the solvent displacement technique to improve the bioavailability of drugs in the brain. Musumeci et al. conducted a study in which they administered oxcarbazepine (OXC) loaded into PLGA NPs intranasally and found that it decreased the interval needed for a therapeutic effect from 24 hours to 1 hour when compared with the drug alone. This was evidenced by the decreased frequency of seizures in rats [31].

9.6.1.2 LIPIDIC

9.6.1.2.1 Liposomes

Liposomes fall under the category of organic NPs. They are spherical in shape and biocompatible in nature. Liposomes are very effective and compliant drug delivery systems made from a lipid bilayer. They have an impermeable external lipophilic phospholipid layer and an aqueous core

that helps transport lipid-soluble substances into cell membranes through the phospholipid layer. Hence, they have the ability to transport a variety of bioactive chemicals within or outside of the particle. Agents enclosed in liposomes provide improved protection against quick destruction caused by the external environment. Liposomes reduce drug toxicity from introduction to non-target locations and improve therapeutic efficacy [47–49, 53]. An important investigation into the capability of multifunctional liposomes to target A was carried out by Balducci et al. These liposomes were dual-functionalized with phosphatidic acid (PA), a high-affinity ligand for Aβ, and mApoE to facilitate BBB crossing. There *in vivo* research findings, which found that mApoE-PA-LIP reduced amyloid plaque burden, are helpful for treating AD [54]. Mortous et al. developed multimodal liposomes with a strong affinity for amyloid plaques and clinical applications. They produced liposomes including a curcumin analog and a BBB transport activator (anti-transferrin antibody (TrF)) [53]. According to Saffari et al., metformin and phosphatidylserine liposomes were administered together as neuroprotective drugs to treat AD diseases. The produced nanoliposomes had a 39% encapsulation effectiveness and a 150 nm particle size. The composition decreased cytokine levels associated with neuroinflammation and cell death, improved memory and cognition in AD rats, and efficiently targeted the brain [55].

9.6.1.2.2 Solid Lipid Nanoparticles (SLN)

The modern delivery method known as SLN has solid lipid as its primary core and a biodegradable surfactant as its outermost surface. SLN's high drug-carrying capacity, compact size, larger enhanced surface area, better stability than other lipid carriers, compatibility with a diverse range of treatments, lowest toxicity profile, and solubility and permeability increase are only a few of its distinctive qualities. SLN is suited for all other kinds of bioactive and is primarily chosen for delivering proteins, peptides, and other hydrophobic medicines with high molecular weights. These are being thoroughly investigated at the moment for designing new medicines to treat different neurological illnesses including AD. Sathya et al. described how α-Bisabolol was a natural neuroprotective and antioxidant agent that was used to reduce Aβ aggregation and neurotoxicity. They used a hot homogenization process to create SLN by utilizing soy lecithin, tween 80 and cholesterol. α-Bisabolol had a greater affinity for binding to the lipid matrix, which improved drug encapsulation and reduced degradation during

the encapsulation process. The system significantly reduced AChE activity, oxidative stress, and neurotoxicity, resulting in lessened Aβ aggregation [56]. Graverini et al. utilized an emulsification method that used Compritol 888 ATO and Brij 78 to create an andrographolide-loaded SLN to achieve neuroprotective and antioxidant effects. The drug-enriched lipid shell caused the carrier to release quickly. Packaging andrographolide into nanocarriers increased its penetration into cells. The formulation was administered to rats, and there was no microglia response, indicating that the brain macrophages did not regard the SLN as foreign objects. The study concluded that the SLN greatly enhanced both the drug's bioavailability and brain targeting [57].

9.6.1.3 METALLIC

Metal-based nanoparticles are used to treat Alzheimer's disease less frequently than polymeric nanoparticles and lipid-based carriers. Metal nanoparticles range in size from 1 to 200 nm and exhibit unique physical and chemical properties depending on their size and shape. Metallic NPs come in a variety of forms, including gold, silver, titania, and others [29].

9.6.1.3.1 Selenium

Xinlong Huo et al. formulated curcumin-loaded selenium nanoparticles poly-lactide-co-glycolide (PLGA) nanocomposites using an emulsion solvent evaporation technique. To study the impact of reducing Aβ plaque aggregation and reducing inflammation on AD pathology, the transgenic 5XFAD animals were given Cur-loaded Se-PLGA nanoformulations. The findings of the study show that Cur/Se-PLGA nanoformulations can effectively inhibit Aβ plaques [58].

9.6.1.3.2 GOLD

Nan Gao et al. fruitfully developed AuNPs@POMD-pep (AuNPs: gold nanoparticles, POMD: polyoxometalate with Wells–Dawson structure, pep: peptide) which act as an Aβ inhibitor, inhibiting Aβ aggregation, separating Aβ fibrils, reducing Aβ-mediated peroxidase activity, and Aβ-induced cytotoxicity. These effects are all achieved through the synergistic action of AuNPs@POMD-pep. They can traverse the BBB and thus overcome

limitations of small-molecule anti-AD drugs by utilizing AuNPs as BBB-crossing vehicles [59].

9.6.2 CHARGE DEPENDENT

The blood-brain barrier (BBB) is one of the most important defense systems in the central nervous system. It has several distinctive defensive mechanisms. The paracellular gap for cells and substances is blocked by the tight connections between brain endothelial cells, which act as a physical barrier. This barrier restricts the flow of infections or poisons and selectively permits particular molecules, such as tiny lipid-soluble molecules, to pass through the capillary endothelial membrane. However, because it severely impedes medication delivery during a disease state, it becomes a significant challenge [46, 60]. The brain consists of negatively charged micro-vessel endothelial cells. The microvascular endothelial surface's complex structural composition and negative surface charge control the passage of big macromolecules and therapeutic medicines into the CNS. Charge can alter a molecule's permeability through the BBB by influencing its affinity for certain transporters, protein binding, or adsorptive-mediated transcytosis, among other ways [45].

The charge on nanoparticle surface serves a significant role in the delivery of the drug into the brain safely and without cytotoxicity. To minimize the possible toxicity, the charge-dependent nanoparticles should be delivered carefully into the brain [43, 46]. The cationic nanocarriers are more desirable for CNS drug delivery, while weak electrostatic repulsive interactions between individual particles are the cause of the poor aggregation stability seen for NPs with negative surface charges. API nanocarriers with large positive surface charges are also unfavorable (even though they are comparatively easy to phagocytize as compared to NPs) since they were shown to have an immediate harmful impact on the blood-brain barrier (BBB) [61]. For instance, Saini et al. successfully demonstrated efforts to distribute ferulic acid across the barrier using chitosan-coated SLNs (solid lipid nanoparticles). SLNs are delivered through the intranasal route, then observed *in vivo* as well as *in vitro*, and came to the conclusion that the SLNs without coating had a lesser ferulic acid concentration in the brain (5.42 folds) compared to chitosan-coated SLNs (6.91 folds). This is because adding positive charges to the surface of nanoparticles using polymers like chitosan prolongs their residence duration and reduces opsonization [62].

Thus, to optimize the blood circulation duration and prevent BBB toxicity, AD treatment NPs should have a tiny positive charge on their surface.

9.7 SMART DRUG DELIVERY SYSTEMS

Apart from the already documented methods, smart drug delivery approaches are the most recent and advanced methods requiring the use of delivery vectors that have high affinity for LDL, GLUT-1, LAT-1, or lactoferrin or transferrin receptor (TfR) to enable receptor-mediated transcytosis across the BBB. The use of brain targeting peptide is another method to increase the drug titre in the brain, which can be helpful in treating brain malfunctions such as AD. However, all are designed to increase the drug titre in the effective organ, i.e., the brain, irrespective of the condition. Though, still the low transport across the BBB is considered a challenge. Another crucial aspect of AD is the generation of Reactive Oxygen Species (ROS) which tend to manifest oxidative damage to the surrounding tissue resulting in neuroinflammation and degeneration. Hence, controlling ROS is another aspect to regulate AD progression [63]. Conventionally, there are many herbal drinks that are gaining popularity due to their antioxidant potential, but again the dose with respect to brain bioavailability is still a concern. Hence, researchers have tried to combine the two strategies.

On similar lines, Zang et al. have utilized the phagocytic inhibiting marker CD47 to formulate longer circulating drug delivery carriers [64]. Microglia are brain disease-associated macrophages that are chronologically activated in brain diseases such as AD, which sequentially increases neurodegeneration due to a higher ROS load. CD47 was used to inhibit the action of these macrophages and deliver the RIPK1 inhibitor Nec-1s to microglia, resulting in a marked reduction in Aβ burden, movement of activated microgliosis and astro cytosis, and thereby reducing oxidative stress in AD. Similarly, bio-actives with metal NPs such as selenium, nickel, etc., have also been tried to decrease the oxidative burden in AD [65]. In neurological diseases, mitochondrial oxidative stress is a key pathological factor. To address this issue, Kwon et al. formulated ceria NPs surface-conjugated with triphenyl phosphonium as a mitochondrial targeting agent, where CeO_2 NPs functioned as sturdy and recyclable ROS scavengers by shuttling between Ce^{3+} and Ce^{4+} oxidation states. *In vivo* studies proved the anti-AD potential [66]. Gao et al. also worked on similar lines and proved the higher efficacy of selenium-chondroitin sulfate NPs in attenuating

ROS oxidative stress, protecting the cytoskeleton, and helping to reduce hyperphosphorylation of tau [67]. Likewise, many other scientists have also proven the same [68–70].

Similarly, ultrasound is also being used in paving the way for drugs to reach the brain through a localized cavitation mechanism. However, it can result in damage to the BBB, but with careful selection of ultrasonic wave strength, one can facilitate drug entry into the brain. Consequently, cavitation helps in brain imaging [71]. Liu et al. have utilized the "sonoporation" effect of ultrasonic waves for delivering quercetin to the brain parenchyma for the treatment of AD. Quercetin-modified sulfur NPs have been found to reduce neuronal apoptosis, inflammatory response, and oxidative damage caused by the disease. Further *in vivo* studies have revealed an improvement in learning and memory activities of the animals, highlighting the significance of the developed formulations [72]. However, neuroinflammation is a concern hindering the widespread use of this therapy [73]. Similarly, Mehta et al. have explored magnetic resonance imaging using a gadolinium-based contrast agent in the hippocampus in early AD with the assistance of ultrasound. Additionally, brain delivery through systemic delivery is being replaced by many research groups using brain implants. Daniel et al. delivered nerve growth factor using a brain implant, and the constant release helped achieve the primary endpoint of AD by reducing shrinkage and improving progression in clinical variables [75].

9.8 CONCLUSION

For the treatment of Alzheimer's disease, transporting the drug across the brain by bypassing the BBB is a significant challenge. Physiologically, the BBB is considered to be the most regulated barrier. Hence, it needs special interventions to bypass drugs from peripheral blood to the brain. Traditionally, the intuitive idea was to develop drugs that are lipophilic to get an easy passage to the brain; however, the availability of efflux transporters further complicates the drug delivery scenarios. Traditional drug delivery also failed in this context. Therefore, it calls for new and improved methods to target Alzheimer's disease. Subsequent chapters address the booming smart drug delivery that has the potential to specifically target Alzheimer's disease. It is hoped that upcoming smart therapies can change the paradigm of brain diseases such as Alzheimer's disease and will be helpful to patients who are tirelessly waiting for clinical innovations to happen.

KEYWORDS

- **Alzheimer's disease**
- **blood brain barrier**
- **chitosan nanoparticles**
- **nanoparticles**
- **smart drug delivery**
- **solid lipid nanoparticles**
- **targeted drug delivery**
- **tau protein**

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CHAPTER 10

Nanocargos for Efficient Delivery of Nutraceuticals Across the Blood-Brain Barrier

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ABSTRACT

Aging people all throughout the world frequently suffer from neurodegenerative diseases. The majority are characterized by neuronal loss, protein aggregation, oxidative stress, mitochondrial damage, and neuroinflammation. Despite being widely used, conventional medication for symptomatic treatment has limited therapeutic success for a variety of reasons. Researchers have effectively proved the therapeutic efficacy of plant-derived nutraceuticals as an alternate strategy in cellular as well as animal models of neurodegenerative disorders. Functional foods known as nutraceuticals have been reported to provide basic nutrition and health benefits. These are also employed for prevention and treatment of a plethora of diseased states. Phytochemicals, probiotics, vitamins, antioxidants, and vital minerals that come from plant and microbial sources may also be included in such ingredients. However, due to their limited bioavailability *in vivo* and restricted permeability across the blood-brain barrier, the majority of nutraceuticals failed during clinical studies in human beings. Therefore, the present focus is on enhancing the transport of nutritional supplements to the brain. The development of nanocarriers loaded with nutraceuticals in order to increase bioavailability and therapeutic efficacy in the brain has gained enormous attention. The studies on nanoparticles-based nutraceuticals delivery in

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neurodegenerative illnesses are discussed here, along with their benefits and drawbacks, toxicity, and regulatory issues.

10.1 INTRODUCTION

All life forms inevitably age, a process defined by deterioration in health as well as an increasing risk of dying. Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and frontotemporal lobar dementia (FTD) have all been linked to the aging process as a primary risk factor [1] (Figure 10.1). One of the most common effects of aging is neurodegeneration, which may be linked to epigenetic alterations, impairment of proteostasis, and genetic mutations in the brain's milieu. Out of all the diseases of neurodegeneration, Alzheimer's disease and Parkinson's disease are the most commonly affecting larger populations. Further, with recent advancements in healthcare, a number of new strategies, including neurotransmitter modulation, receptor targeting, stem cell treatments, hormone therapies, etc., have been employed for the management of neurodegeneration *per se*. While much water has flowed under the Thames, particularly in research endeavors, therapeutic uses of such breakthrough tools are still far from reaching the affected patients. Finding a less expensive alternative medication that can be used over the long term to combat these devastating neurodegenerative problems is therefore essential. Thus, improving neuronal health is quite important in this context, and nutraceuticals that can work on numerous targets at once seem to be a promising approach. Nutraceuticals, primarily products of plants, have both medicinal as well as nutritional values. These tend to protect from various chronic diseases for providing and sustaining physiological well-being. Nutraceuticals impede neurodegeneration by changing cellular and molecular processes as well as protein misfolding [2]. Despite the benefits, nutraceuticals have not been successful in humans, owing to low bioavailability, poor absorption, and restricted permeability of nutraceuticals across the blood-brain barrier (BBB). In this regard, novel drug delivery systems are being investigated to improve neuro availability by exhibiting distinctive uptake and absorption mechanisms [3]. Thus, the current chapter furnishes a bird's eye view of various nutraceuticals being employed in neurodegeneration and their delivery systems.

10.2 NUTRACEUTICALS AND NEURODEGENERATION MECHANISMS

Of late, nutrition-based therapeutics, i.e., nutraceuticals, have gained enormous significance owing to their myriad benefits. Multiple pathways have

been identified as causes of neurodegeneration, including mitochondrial dysfunction, oxidative stress, calcium overload, and inflammation [4]. Neurodegeneration is primarily caused by damage to the mitochondria. Two genomes, namely nuclear DNA (nDNA) and mitochondrial DNA (mtDNA), control how mitochondria work [4(b)]. If either of these genomes is mutated, it can lead to neurodegeneration caused by mitotoxicity. The second prominent mechanism involved in neurodegeneration is calcium overload. Generally, calcium is found in higher concentration in the extracellular milieu compared to the intracellular milieu. Thus, there is a strong correlation between the survival of neurons and the maintenance of intracellular Ca^{2+} levels. A sudden rise in intracellular concentrations leads to the activation of various Ca^{2+}-dependent hydrolytic enzymes, which further initiate a succession of neurotoxic events, including mitotoxicity and the halting of ATP production, eventually causing dysfunctional neurons and cell death [5]. Oxidative stress is also known to be a primary cause of neurodegeneration as it damages DNA, RNA, proteins, and lipids, thereby causing neurodegeneration. Additionally, macrophages found in close proximity to glia and microglia in the brain play a crucial function in inflammation-mediated neurodegeneration. By secreting inflammatory cytokines and chemokines, activated microglia play a mediating role in neuronal damage throughout illness [6]. Figure 10.1 depicts the various pathways involved in neurodegeneration.

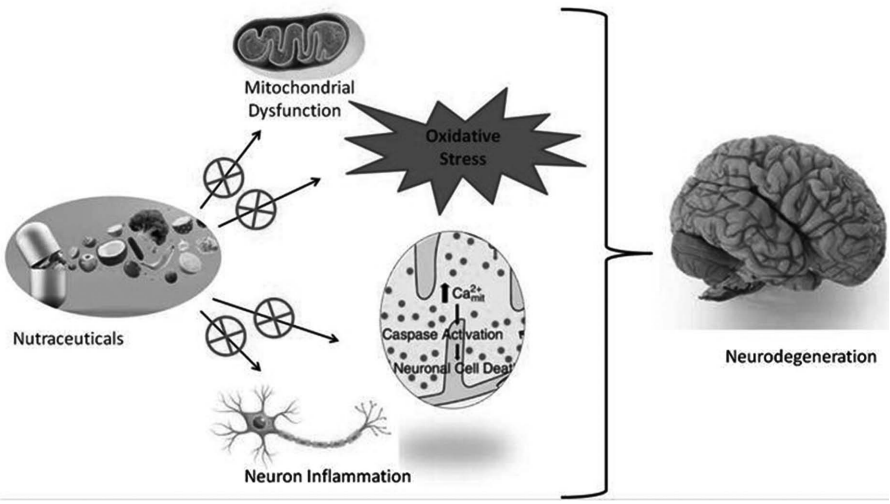

FIGURE 10.1 Various mechanisms involved in neurodegeneration and role of nutraceuticals.

As naturally occurring substances have fewer adverse effects, nutraceuticals in neurodegeneration have been able to present themselves as a superior and safer integrated strategy. Furthermore, these can be used in conjunction with standard medication treatment and the current therapeutic care of neurodegeneration to further boost the quality of life for the patient [7]. The argument for using nutraceuticals is based on the efficacy of various nutraceuticals on several aforementioned pathogenic pathways of neurodegeneration. Thus, nutraceuticals act by amalgamation of more than one mechanism, viz., free radical quenching, mitochondrial homeostasis, anti-inflammation, modification of cell signaling pathways, and metal chelation [8]. The majority of nutraceuticals exert their effects not by adhering to a particular path, but rather by employing a variety of these. Also, nutraceuticals used in neurological diseased states substantiate the saying "let food be your medicine and medicine be your food" by Hippocrates. Various instances of nutraceuticals employed in neurodegeneration treatment have been tabulated in Table 10.1, along with their mechanism(s) of action.

TABLE 10.1 Different Nutraceuticals Employed in Neurodegeneration Management and Their Mechanism(s) to Counteract Neurodamage

Sl. No.	Nutraceutical	Source	Mechanism of Action
1.	Curcumin	Turmeric	Exhibits antioxidant action via Nrf2 and anti-inflammatory action to inhibit neuronal damage [9].
2.	Coenzyme Q10 (CoQ10)	Meat, fish, nuts	Strengthens endogenous antioxidant scheme via Nrf2/HO-1 pathway [10].
3.	Resveratrol	Grapes, berries, nuts	Exhibits anti-protein aggregation and/or anti-amyloidogenic action [11].
4.	Epigallocatechin-3-gallate (EGCG)	Tea leaves	Exerts anti-amyloidogenic action by inhibiting formation of Aβ1-42 amyloid fibril [12].
5.	Polyunsaturated fatty acids	Fish oils, maize, mustard, and grape seed.	Exhibits prooxidant action by inactivating microglia/astrocytes [13].
6.	Vitamin E	Edible oils, particularly wheat germ oil.	Exhibits antioxidant activity [14].
7.	Cyanidin	Red berry, blue berry, cranberry.	Suppresses the activation of pro-inflammatory cytokines [15].
8.	Luteolin	Carrot, pepper, cabbages.	Antioxidant action [16].
9.	Lycopene	Tomatoes, papaya	Reduces ROS, and by inhibits mitochondrial dysfunction [17].

TABLE 10.1 *(Continued)*

Sl. No.	Nutraceutical	Source	Mechanism of Action
10.	Fish oil	Fatty or oily fish such as tuna, trout, salmon.	Anti-inflammation action [18].
11.	Ginsenosides	Found in ginseng	Glutamatergic and monoamine transmission, reduces production of nitric oxide (NO) [19].
12.	Vincamine	Derived from plant Vinca minor.	Reduces oxygen stress levels in brain [20].
13.	Vinpocetine	Semi-synthetic derivative of the Vinca minor.	Improves blood flow in the gray matter of the brain [21].
14.	MitoQ	Derivative of coenzyme Q10, conjugated to triphenyl phosphonium cation.	Upregulates the expression of Nrf2 downstream protein [22].
15.	Mito-apocynin	Triphenyl phosphonium conjugated derivative of apocynin.	Improves dysfunctional Mitochondria and exerts antioxidant action [23].

10.3 ENCEPHALIC DELIVERY OF NUTRACEUTICALS

The blood-brain barrier, often known as the BBB, is a barricade that stops most medications/xenobiotics from entering into the brain. It is composed of a partially permeable membrane barrier and is located at the point where the blood supply meets the tissue of the brain [24]. The majority of nutraceuticals have not been successful in clinical trials conducted on humans owing to their poor permeability across the BBB, leading to poor *in vivo* neuro availability. Furthermore, low intestinal permeability, poor solubility in the gastrointestinal tract, and hepatic first-pass metabolism are the major challenges contributing to poor bioavailability of nutraceuticals. This makes them less likely to be absorbed by the body. Thus, the focus of researchers has been on developing methods to enhance the encephalic delivery of nutraceuticals [25]. In this context, a lot of emphasis has been paid to the research and advancements of nanocarriers and/or nanoparticle-conjugation to nutraceuticals, with an objective of escalating both the bioavailability in the brain and their therapeutic efficacy [26].

Nanocarriers are the chemical entities varying in different size ranges from 1 to 100 nm in one dimension. Nanocarriers can further be subdivided into categories based on composition, namely, lipid-based, polymer-based, carbon-based, and inorganic material-based nanoparticles [27]. Nanocarriers

have several advantages over conventional drug delivery systems. Due to their high surface area to volume ratio, they can improve the pharmacokinetics and biodistribution of therapeutic agents, leading to reduced toxicity and preferential accumulation at the target site [28]. They can also enhance the solubility and stability of hydrophobic compounds, including drugs, bioactives, peptides, and oligonucleotides, making them suitable for administration to achieve optimum therapeutic effects. Additionally, nanocarriers can be used to deliver drugs to the central nervous system, which is normally protected by the blood-brain barrier (BBB). Although the BBB plays a critical role in preventing harmful agents from entering the brain, it also makes it difficult for drugs to reach the CNS and treat neurological disorders. However, using nanocarriers facilitates the penetration of drugs across the BBB as well as bypassing Pgp efflux [29].

The use of a different route other than the oral or vascular route to deliver nanocarriers could be a useful addition to nanotechnology in order to improve the effectiveness and bioavailability of the compounds at precise sites in the body. Further to various routes available for drug delivery to the brain, the nose-to-brain route has been finding promising results. Various studies have been undertaken to improve the neuro availability of drugs and/or bio-actives using various nanocarriers through the intranasal route. The intranasal (IN) route gives direct, non-invasive access to the brain by avoiding the barrier. It avoids bloodstream clearance and invasive methods. This increases the amount of the bioactive that gets to the central nervous system and decreases the side effects too. Also, the route being painless is easy on the patient and makes the drug work better [30]. Hadel et al. [31] have overlaid lipid nanocarriers with berberine for intranasal route delivery. The researchers found out that Berberine brain/blood levels were higher vis-a-vis plain berberine solution (IN), suggesting enhanced brain targeting. Likewise, the co-delivery of curcumin and quercetin via intranasal route has been found to achieve superior efficacy in targeting the brain as compared to the naive drug solutions individually as well as in combination [30]. Also, the potential of nanocarriers loaded with ferulic acid in AD management has been investigated, and significant augmentation in cognitive performance of animals was noticed [33].

10.4 LIPID-BASED NANOCARGOS

Nanocarriers made of lipids have been a breakthrough in the domain of medicine delivery. The reason these nanocarriers have succeeded in getting

so much interest over the last few years is partly because the lipids they are made of have favorable characteristics, like being biocompatible and exhibiting a low level of toxicity [34]. Lipid-based nanocarriers have been used for improving the clinical potential of bio-pharmaceutically limited drugs and/or nutraceuticals, such as those that don't dissolve well in water or aren't stable, and to offer alternatives to the parent route. More specifically, the ease of use and benefits of the oral route, like how easy it is to give the drug and how well patients follow directions, have made research on lipidic nanocarriers more important. The major lipid-based delivery systems include liposomes, self-nano, and micro-emulsifying delivery systems, nano-emulsions, and nano-capsules [35]. Lipid-based nanocarriers can improve nutraceutical delivery from the nose to the brain as these can protect the nutraceutical inside from being broken down by biological and/or chemical processes and from being taken out of the cell by P-gp efflux proteins. Also, bio-adhesion of lipidic carriers to keep the active constituent on the mucosal surface of the nasal cavity, and their ability to temporarily open the tight junctions of the mucosal epithelium tends to improve bioactive delivery to the brain. The lipid-based nanoparticles move from the nose to the brain through the mucosa by going through olfactory neurons and different endocytic pathways of glial cells [36].

10.5 POLYMERIC NANOCARGOS (PNCS)

Recently, PNCs have been used a lot as biomaterials because they are simple to fabricate and design, and are biocompatible [37]. These are available in a wide range of structures, and behave akin to living things. This is quite lucid in smart drug delivery, where PNCs play a major role by delivering the active ingredient to the right site in the body in a very efficient way. Further, in terms of getting nutraceuticals to where they are intended to go, PNCs are easy to combine with other strategies as well. Also, they have the potential of targeting the specific organ or tissue at the right concentration. Moreover, the nutraceuticals as volatile active ingredients are provided with stability and a relatively long duration of action [38]. Similar to lipidic nanocarriers, for drug delivery from the nose to the brain, different types of polymeric nanocarriers have also been looked into. Polymeric carriers being safe, capable of encapsulating drugs well, and with varied composition and structure choices to increase mucoadhesiveness and slow down mucociliary movement, enable them to stay in the nasal mucosa for a longer duration.

They can also have permeation-enhancing properties that increase paracellular permeability across the nasal epithelium by temporarily opening tight junctions of the brain [39].

10.6 CARBON-BASED NANOCARGOS

Carbon-based nanomaterials have certain qualities, like a large surface area, good mechanical and electrical properties. These qualities make them useful in the therapeutic as well as diagnostic fields. Carbon nanotubes, nanodiamonds, fullerenes, carbon dots, etc., are the delivery systems explored for the delivery of nutraceuticals [40] in the management of neurodegeneration. Electroconductivity of MWCNTs could be employed to deliver the bio-actives to a specific region of the brain, like the limbic region, which is where most neurodegenerative diseases start to worsen [41].

10.7 INORGANIC NANOCARGOS

Inorganic NPs, including silver, gold, and other metal oxide NPs, have optoelectronic and dielectric properties that have drawn the attention of scientists because they could be used in biomedicine [42]. Most of the time, silver, iron oxide nanoparticles (IONPs), and titanium dioxide nanoparticles are employed in bioimaging for the diagnosis of diseases. On the other hand, some inorganic NPs, like gold NPs and silica NPs, have been explored as nanocargos for targeting the brain [43]. Furthermore, inorganic NPs tend to provide long-term increased permeability and a retention effect, thus making them a good choice for treating brain disorders, including neurodegeneration.

Table 10.2 provides the list of literature instances where the nanocargos have been explored for efficient delivery of various nanocargos. Figure 10.2 portrays the significance of nanocargos in penetrating BBB.

10.8 NANOCARRIERS RELATED POTENTIAL RISK FACTORS

As nanocarriers have been established as a breakthrough strategy to reach the BBB, several issues still need to be resolved. The particular distribution of large nanocarriers to the brain is not well understood in most studies

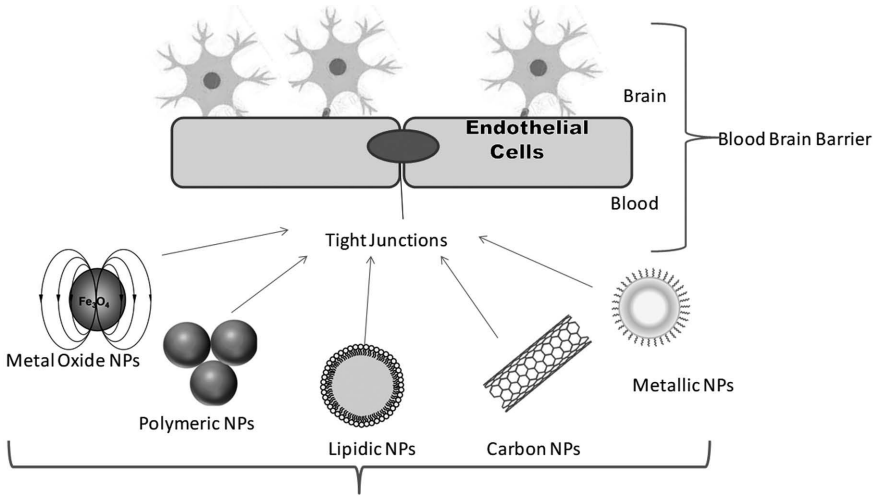

FIGURE 10.2 Role of nanocarriers in crossing tight junctions (BBB) of brain.

TABLE 10.2 Various Nutraceuticals and Their Nanocargos Explored for Efficient Delivery to Brain

Sl. No.	Nutraceutical	DDS	Inference
		Lipid-based Nanocarriers	
1.	Curcumin	SLNs	Cur-SLNs at high dose improved neuro generation by combating oxidative stress [44].
2.	Chrysin	SLNs	Mitochondrial uncoupler and mitigated neurodegeneration possibly via PINK1/Parkin mitophagy [45].
3.	Epigallocatechin-3-gallate (EGCG)	Nano-lipidic delivery system.	Improved *in vivo* oral bioavailability by more than two-fold over free EGCG [46].
4.	Quercetin	Liposomes	Improved neuroprotection by reducing oxidative stress [47].
5.	Resveratrol	NLCs	Improves the ROS-induced mitochondrial dysfunction [48].
6.	Curcumin	SNEDDS	Improved neuroprotection in a dose dependent manner [49].
		Polymeric Nanocarriers	
7.	Q10	Trimethylated chitosan-conjugated PLGA.	Potential to transverse the blood–brain barrier for neuroprotection and low toxicity [50].
8.	Piperine	Chitosan NPs	20-folds decrease in oral dose, and decreased morbidity [51].

TABLE 10.2 *(Continued)*

Sl. No.	Nutraceutical	DDS	Inference
		Carbon Nanocargos	
9.	Curcumin	Carbon dots nanocomposite	Slow down the production of reactive oxygen species (ROS), thereby restoring nerve damage and maintained neuronal morphology [52].
10.	Curcumin	Graphene oxide-like carbon-based nanoparticles.	Nontoxic nanocarrier for the delivery of CUR with good biosafety [53].
11.	Quercetin	CNTs	Ameliorates MWCNT-induced neurotoxicity through antioxidant, anti-inflammatory, and anti-pyroptotic mechanisms [52].
		Inorganic NPs	
12.	Lactoferrin	Magnetic nanoparticles	*In-vitro* and *in-vivo* experimentation revealed enhanced ability of Fe_3O_4-Lf probe to cross the BBB [54].
13.	Quercetin	SPIONs	Enhanced the bioavailability of quercetin in the brain about 10 folds higher than free quercetin [55].
14.	Extract of *Lampranthus coccineus* and *Malephora lutea*	Silver nanoparticles	Combat oxidative stress to decrease neurodegeneration [56].

[57], and that could possibly pose harm to any organ. An important factor is how nanocarriers are metabolized, particularly the inorganic nanocarriers, as inorganic materials like iron, gold, and silica are difficult to metabolize and are likely to get deposited in the brain [58]. Also, according to prior studies, biodegradable nanoparticles are prone to exhibit neurotoxicity [59]. For instance, after chitosan nanoparticles modified with polysorbate 80 were injected into the body, it was discovered that the body weight significantly decreased over the course of seven days in a dose-dependent manner, as well as causing neuronal apoptosis, necrosis, and a mild inflammatory response in the frontal cortex [60]. While most pharmaceutical preparations in general are administered orally, the majority of nano-formulations are administered by injection. In practice, oral preparations are more tolerable than injections, particularly for people with neurological illnesses. Therefore, additional research needs to be conducted in the domain, including additional investigations on the potential long-term and acute neurotoxicity.

10.9 TOXICITY CONCERN AND SAFETY EVALUATION

The safety concern for this nano-system is doubtful despite the alluring promise of these nanocarriers holding nutraceuticals which have both advantages of the neuroprotective effects of nutraceuticals and physicochemical features of nanoparticles. There is a dearth of evidence-based research on biological systems' absorption, distribution, clearance, and toxicity. Research has shown that nanoparticles (noble metal) might prevent dietary supplements including epigallocatechin gallate, gallic acid, and vitamin C from scavenging hydroxyl radicals, leading to the formation of ROS and ultimately cell death [61]. The presence of component surfactants in some nano-delivery systems, which might enhance permeability and change the integrity of the BBB, can make them hazardous [62]. Nano-system components including antibodies, drugs, biomolecules, linkers, and probes may behave as antigens and cause neurotoxicity. It is also difficult to understand the mechanism of nutraceutical-drug interactions because of the complicated nature of the nutraceutical and nanoparticle system. Guidelines have been suggested by the European Food Safety Authority (EFSA) to assess toxicity caused by the substitution of nanoparticles [63]. Accepting this idea in drug development helped to lower drug removal risks from 50% to 20%. The basic characterization of nanoparticle characteristics, such as size, crystal structure, surface area, shape, hydrophobicity, solubility, and dispersion state, serves as the basis for the toxicity assessment. For the purpose of determining toxicity, a variety of animal and cellular models are used. These models include (i) toxicity analysis (*in vitro*), which consists of localization studies and cell uptake; (ii) cell feasibility assays, which measure necrosis, apoptosis, and cell proliferation; and (iii) studies related to mechanistics, which measure oxidative stress and DNA damage [64]. Despite the fact that researchers have looked into *in vivo* and *in vitro* investigations of numerous nano-formulations in diverse model systems, systemic assessment remains a key concern, and the assessment of nanotoxicity in slaughtered animals is yet indeterminate.

Additionally, there are no established guidelines or conventional toxicity evaluation techniques to establish the toxicity and negative consequences of nano-based carrier systems. The current production standards for nutraceuticals on the international market are insecure. Although the World Health Organization (WHO) and the United Nations Food and Agricultural Organization (FAO) have printed some guiding principles for the safety and quality check of nutraceutical products, there is no universally accepted terminology or classification system, and there are no standardized policies that govern the production and marketing of these nutraceuticals [65]. The majority of

these items are marketed as safer medicines than synthetic ones and are offered on the market with little control.

10.10 NUTRACEUTICALS: REGULATORY PERSPECTIVE

The definition of nutraceutical tends to overlap with that used for food supplements. There is an ardent need to address the discrepancies among the various definitions of nutraceuticals, and regulatory aspects are a significant challenge. Nutraceuticals have been going through a dark phase in terms of their regulations. Thus, it is quite significant to underline their clear usage, specificity, and utility. As nutraceuticals fall between medicines and medicinal food, stakeholders may find it harder to get health claims clearance. There are hardly any common regulatory guidelines for nutraceutical globalism, as the prevalence of multi-country guidelines tends to cause chaos in maintaining uniformity globally [65].

The Food Safety and Standards Act (FSSA) came into existence in 2006 in India and was laid down to maintain the availability of food products in the nation, including their production, storage, distribution, sale, and import. According to the FSSA act, nutraceuticals fall under the category of foods formulated to satisfy specific nutritional requirements that exist due to some diseases and disorders, defined as "foods for special dietary uses" or "functional foods" or "nutraceuticals or health supplements" by Section 22(1) of the FSSA. Similarly, the various other regulatory guidances, such as EFSA (EU), Dietary Supplement Health and Education Act (DSHEA; USA), and Natural Health Products Regulations (NHPR; Canada), lack harmonization throughout the world [32]. Thus, to reinforce consumers' trust in nutraceutical products, there should be the implementation of a standardized, research-driven regulatory framework.

10.11 FUTURE PERSPECTIVES

It is possible for nutraceuticals to be properly delivered and released inside the targeted cells with the use of nanocarriers in therapeutic delivery systems. Despite the fact that nanocarriers have substantially facilitated brain targeted delivery studies over the years, neither of these nanocarriers has been issued market authorization after successfully completing all rounds of clinical testing. The advantages of nanocarriers mentioned above highlight the need to expedite their translational advancement into clinical practice; however, advances in technology must be spearheaded to accomplish appropriate

capacity for application performance and the manufacturing of cost-effective affordable pharmaceutical formulations. Furthermore, it is crucial to support new nano-nutritional formulations with experimental and scientific data. In due course, standardized rules, experiment layout, and human testing should serve as the basis for the determination of safety and efficacy profile. The creation of innovative nanotechnology-based nutraceuticals with better quality, safety, stability, and effectiveness will be the focus of future research era. Additionally, efforts need to be poured in to deal with the issue of nano-toxicity and non-uniformity of guidance globally.

10.12 CONCLUSION

Designing and creating nanocarriers loaded with nutraceuticals for the management of neurodegenerative conditions has grown in priority as a research area. However, the majority of nutraceuticals have issues with instability, low water solubility, pharmacokinetics, and bioavailability, which prevent their use in clinical applications. To address this, nutraceuticals and nanoparticles have been combined to increase the bioavailability of drug products by enhancing the penetration of the BBB, thus enhancing the effectiveness of neurodegenerative treatments. Additional studies should be conducted for quality control of nanoparticles and to address toxicity issues in human clinical trials. Stringent guidelines should be followed for the commercialization of nutraceuticals, along with adherence to standards for production and distribution in the global market. A global regulatory framework that clearly specifies quality, efficacy, mechanism of action, and regulatory standards for such products could enable customers and the market, which is essentially required.

KEYWORDS

- **global market**
- **nanocarriers**
- **nanoparticles**
- **neurological disorders**
- **nutraceuticals**
- **phytoconstituents**
- **regulations**

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CHAPTER 11

Recent Advancements in Strategies for Delivery of Neuro-Nutraceuticals to the Brain

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ABSTRACT

A significant part of the world's population, especially the aged, is prone to several neurodegenerative diseases that usually affect memory, cognition, attention, concentration, and other mental functions. Major neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and senile dementia, are marked by the loss or damage of specific neurons, the accumulation of faulty protein aggregates, marked oxidative stress, and neuroinflammation. Several synthetic molecules,

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especially nootropics (e.g., Piracetam), anti-parkinsonians (e.g., Levodopa and Amantadine), and anti-Alzheimer's agents (e.g., Donepezil, Galantamine, and Rivastigmine), are in clinical practice but despite their persistent long use, the satisfying outcomes are still awaiting. Moreover, being synthetic molecules, such drugs exert many side effects such as sedation, altered motor functions, restlessness, affected behavior, etc. Such synthetic molecules provide on-and-off results but fail to cure completely, so there is a need to find alternative therapy which is chiefly dedicated to phytomedicines, particularly neuro-nutraceuticals, probably due to their holistic aspects and lesser side effects. Nowadays, nutraceuticals have evolved as a promising approach for neurological degenerative diseases, but the poor bioavailability and restricted permeability across the blood-brain barrier challenge their beneficial effects for clinical purposes. This chapter is focused on the development of new strategies such as lipid-based carrier systems, nanoparticle-conjugated nutraceuticals, nanostructured lipid carriers, etc., for delivering neuro-nutraceuticals to the brain. These recent strategies can improve the efficacy of neuro-nutraceuticals by increasing bioavailability, modulating the drug-release profile, bypassing the first-pass metabolism, etc. The challenges involved in the development of novel delivery systems of neuro-nutraceuticals to combat neurodegenerative disorders are also considered and included.

11.1 INTRODUCTION

Globally prevalent neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) affect millions of people worldwide. Neurodegenerative disorders generally refer to the loss of functions or death of nerve cells over time. Some therapeutic strategies for managing symptoms of these neurodegenerative disorders are available and in practice. Despite long-term use, synthetic molecules like nootropics, anti-parkinsonians, and anti-Alzheimer's agents in clinical practice have not shown satisfying outcomes. These drugs have side effects such as sedation, altered motor functions, and affected behavior. They provide inconsistent results and do not cure completely. There is a need for alternative therapies, focusing on herbal medicines and neuro-nutraceuticals, due to their holistic nature and fewer side effects. Nutraceuticals act by enhancing the cholinergic system with the inhibition of acetylcholinesterase and also have antioxidant, anti-hypercholesterolemia, and anti-inflammatory properties [1]. Nutraceuticals

have beneficial effects for neurological disorders but low bioavailability and water solubility and restricted entry to the blood-brain barrier (BBB) are main hurdles for the delivery to the specific site. These factors affect the therapeutic effect of nutraceuticals. To overcome these challenges, nutraceuticals are encapsulated for protection against harmful external factors, their incorporation into food products (e.g., increasing the solubility/dispensability of lipophilic compounds in water-based environments), and the maintenance of their maximum therapeutic properties so that they are stable in their bioactive form until they reach the site of action. The above-mentioned challenges can be overcome by employing the nanoformulations of nutraceuticals. Because of this, delivery systems at the micro- and nano-scale have attracted significant attention in recent years. Additionally, in recent years, many methods have been employed and prominent progress has been seen in the arena of delivery systems to improve the bioavailability which in turn improves the effectiveness of nutraceuticals.

11.2 NEUROLOGICAL DEGENERATION

The loss of neuronal functions or neuronal death mediated by progressive neuronal atrophy is referred to as neurodegeneration. The reasons for neuronal damage are protein misfolding and aggregation, oxidative stress, excitotoxicity, and mitochondrial dysfunction. Protein misfolding and aggregation are the first steps for neurodegeneration. Misfolded proteins form large aggregates due to exposure of hydrophobic residues on the surface of proteins that ultimately lead to neuronal death. Oxidative stress, mitochondrial dysfunction, apoptosis, and excitotoxicity also lead to neuronal death. Excitotoxicity, a complex process triggered by excitatory neurotransmitters especially glutamate, leads to neuronal degeneration followed by cell death. Oxidative stress, a state of imbalance in the levels of highly reactive oxygen species (ROS) and free radical scavengers especially antioxidants, is also a significant contributor to neuronal death.

Neurodegenerative diseases include amyotrophic lateral sclerosis, multiple sclerosis, PD, AD, Huntington's disease, multiple system atrophy, and prion diseases. Some neurological disorders shown in Figure 11.1 are focused on and discussed in this chapter. PD and AD are the most common neurological disorders which generally involve abnormal misfolding of proteins, e.g., α-synuclein is involved in PD, and TAR DNA binding protein-43, τau proteins, and amyloid-β (Aβ) are involved in AD. Some commonly

reported factors supposed to be involved in neurodegeneration are depicted in Figure 11.2.

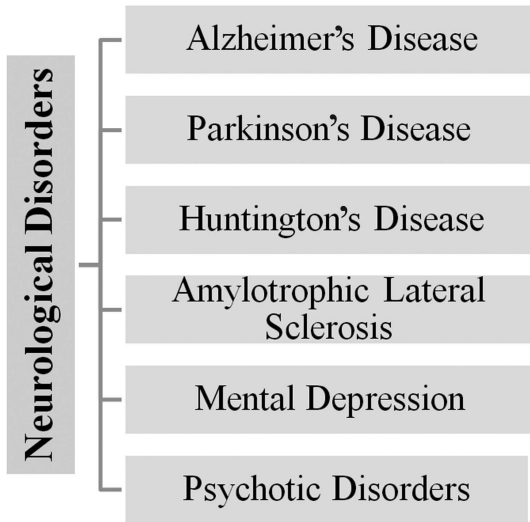

FIGURE 11.1 Focused neurological disorders.

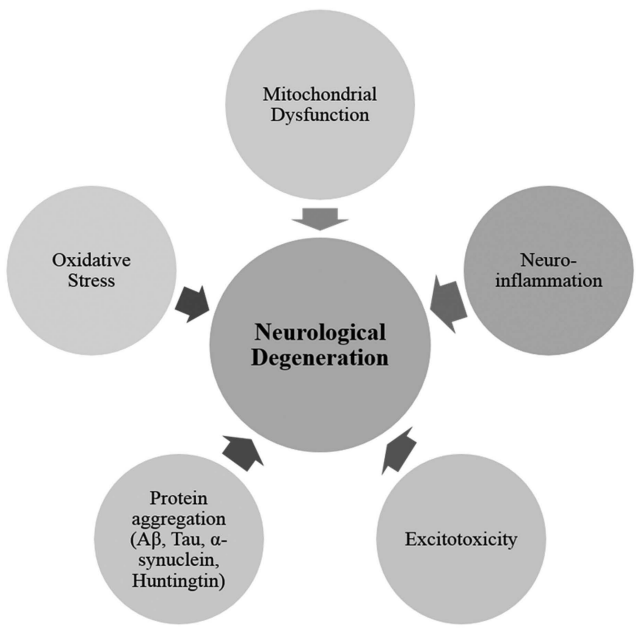

FIGURE 11.2 Neurodegeneration promoting factors.

11.2.1 ALZHEIMER'S DISEASE (AD)

The most prevalent form of chronic neurodegenerative disease, AD, characterized by loss of memory, is considered to involve neurodegenerative changes in subcortical structures and varying regions of the cerebral cortex, especially the temporal lobe, parietal lobe, and portions of the frontal cortex and cingulate gyrus [2]. Amyloid plaques and neurofibrillary tangles develop in this illness. The tiny peptides that make up plaques are known as amyloid beta (Aβ), and they are typically 39–43 amino acids long. Aβ is a portion of the transmembrane protein known as amyloid precursor protein (APP), which enters the membrane of the neuron. In healthy neuron growth, survival, and post-injury repair, APP appears to play functions [3, 4]. Enzymes like gamma-secretase and beta-secretase break APP into smaller pieces [5]. One of these pieces produces amyloid beta fibrils, which can then self-assemble into dense extracellular amyloid plaques [6, 7].

11.2.2 PARKINSON'S DISEASE (PD)

Parkinson's disease (PD) is a prominent neurodegenerative disorder marked by an imbalance in dopamine and acetylcholine neurotransmitter levels, believed to result from damage to neurons in the substantia nigra region of the brain. A significant depletion of dopamine and elevated acetylcholine levels have been reported in PD, which leads to bradykinesia, akinesia, stiffness, resting tremors, postural instability, and other associated symptoms. The physiological factors associated with degeneration of dopaminergic neurons are mitochondrial dysfunctions, oxidative stress, and depletion of antioxidants [8]. It has been observed that Lewy bodies show accumulated complexes and aggregates of alpha-synuclein-ubiquitin. The α-synuclein buildup in Lewy bodies might be caused by impaired axonal transport of the protein [9].

11.2.3 HUNTINGTON'S DISEASE

Huntington's disease is an inherited disorder resulting in brain degeneration, causing severe motor symptoms such as rapid, jerky movements, especially of fingers, face, or tongue. This disease is due to the expansion of the number of repeats of the CAG sequence in specific genes. The larger the number of repeats, the earlier the symptoms appear.

11.2.4 AMYOTROPHIC LATERAL SCLEROSIS

In Amyotrophic lateral sclerosis, motor neurons degenerate and lead to paralysis and eventual death. Degeneration occurs in upper neurons (projecting from higher centers to the spinal cord) and lower neurons (from the spinal cord to skeletal muscles).

11.3 NEURO-NUTRACEUTICAL AND THEIR REQUIREMENT

Nutraceuticals are compounds from foods and dietary supplements that have therapeutic potential [10–12]. Stephen de Felice coined the term 'nutraceuticals,' which originated from two terms: nutrition and pharmaceutical [13–19]. Neuro-nutraceuticals, including Bacoside A, and Bacoside B, Quercetin, Co-enzyme Q10, and Lycopene, are employed in the management of neurological disorders. They are thought to operate by addressing misfolded proteins and modifying cellular cascades associated with neurodegeneration. They have several therapeutic properties associated with neuroprotection such as anti-inflammatory, antioxidant, and anti-hypercholesterolemic, strengthening the cholinergic system by inhibiting acetylcholinesterase, etc. [20].

Nowadays, these natural therapeutic agents are gaining more interest as an alternative treatment for neurodegenerative diseases due to the side effects of synthetic therapeutic agents, such as Galantamine, Rivastigmine, and Tacrine, statins like Rosuvastatin and Atorvastatin.

These nutraceuticals possess the following advantages:

1. Easily available in dietary constituents and formulae [21].
2. As over-the-counter medicines, they are accessible and can be purchased from convenience stores or pharmacy counters [22].
3. More secure and won't have any noticeable negative effects when used on humans [23].
4. May offer a variety of health benefits, including the treatment and prevention of numerous neuropsychological disorders as well as chronic disorders such as diabetes, cancer, heart disease, hypertension, musculoskeletal problems, atherosclerosis, and hypertension [22].
5. Nutraceuticals play an important role in maintaining overall health by slowing down and preventing frailty in the aged.
6. Nutraceuticals are naturally occurring, culturally ingrained in the target society, and free of stigma associated with using manufactured pharmaceuticals; nutraceuticals may be positively received by every group.

11.4 NUTRACEUTICALS IN NEUROLOGICAL DISORDERS

Nutraceuticals can be used for neurological disorders due to having properties such as antioxidants, anti-inflammatory with enhanced cholinergic system, and anti-hypercholesterolemia. Some regularly used nutraceuticals in managing neurodegenerative diseases are shown in Table 11.1 [24–26].

TABLE 11.1 Some Nutraceuticals Used in Neurological Disorders

Alzheimer's Diseases	Parkinson's Disease	Depression	Psychosis
Flavonoids:	Polyunsaturated fats:	Polyunsaturated fats:	Polyunsaturated fats:
Quercetin	Omega 3FA	Omega 3 FA	Omega 3FA
	Carotenoid pigment		
	Lycopene		
Flavons	Steroid glycoside:	Elements:	
Kaempferol flavon	Ginsenoside	Zinc	
Catechin flavons	Alkaloids:	Amino acids:	
Epicatechin	Vincamine	L-Tryptophan, 5 HTP	
Epigallacatechin		Vitamins:	
Luteolin		Vitamin D	
Cyanidin		Folic acid	
Epigallacatechin			
Gallate			

11.4.1 NUTRACEUTICALS IN ALZHEIMER'S DISEASE

The aging process and less intake of dietary antioxidants progress and stimulate AD so nutraceuticals that have high antioxidant properties are used for the prevention of the disease. The compounds having high antioxidant properties such as flavonoids, carotenoids, and flavones are hopeful options for the prevention of the diseases. Flavonoids such as catechin, epicatechin, epigallocatechin, and epigallocatechin gallate are mainly used for neurological disorders, especially AD. These act by interacting with the neuronal glial signaling pathway associated with neuronal survival and functioning [27] and also by modulating cerebral flow which helps in neuronal functions mainly affected in AD [28].

Crocin, obtained from saffron (*Crocus sativus* Family: Iridaceae) has been experimentally proven to be involved in the prevention of neurological disorders such as epilepsy, depression, etc. It acts by altering the oxidative

markers level in the brain [29] and improves cognition as assessed by Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog).

Cyanidin obtained from cranberries, strawberries can be used as a neuroprotective agent, it acts by inhibiting phospholipase A2 which is responsible for the communication of pro-inflammatory cytokines and presents outstanding neuroprotection.

In the flavones category, luteolin and apigenin acquire remarkable neuroprotective activity; having the capacity to protect the DNA against hydrogen peroxide-mediated toxicity and inhibit cell damage as well as neuroinflammation in AD.

11.4.2 NUTRACEUTICALS IN PARKINSON'S DISEASE

Nutraceuticals act by various mechanisms including free radical scavenging, mitochondrial homeostasis, iron chelation, anti-inflammation, and anti-apoptosis. Various nutrients, herbal products, and synthetic substances are used for the treatment and prevention of PD. The following nutraceuticals used in the management of PD act by targeting protein misfolding and aggregation, dysfunctions of mitochondria, oxidative stress, etc.

Co-enzyme Q10 (Co-Q10) and fish oil are two nutritional supplements that can be used effectively in the management of PD. In a PD animal model, Co-Q10 reduced 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-mediated toxicity due to its electron-accepting property and inhibited the electron transfer from complex 1 to other complexes.

Lycopene has been demonstrated to raise dopamine (DA) levels in the striatum and to have neuroprotective effects in animals exposed to MPTP. Lycopene's therapeutic effects are due to its antioxidant activity, neurobehavioral deficits, an increase in striatal enzymatic activities especially reduced nicotinamide adenine dinucleotide (NADH), and superoxide dismutase along with enhanced levels of glutathione and decreased levels of malondialdehyde concentrations.

Eicosapentaenoic and docosahexaenoic acids abundantly present in fish oil have been reported to show neuroprotective potentials via a number of mechanisms and are among the omega-3 fatty acids. One of the most prevalent polyphenols, EGCG (Epigallocatechin-3 Gallate), present in *Camellia sinensis*, has been reported to have neuroprotective properties probably due to its capacity to cross the blood-brain barrier. It significantly improves the motor functions and reduces neurotoxicity by improving the levels of neurotransmitters, especially dopamine, in the affected region of the brain.

Numerous research on PD has shown that the ginsenoside found in ginseng (*Panax Ginseng*, Family: Araliaceae) has neuroprotective properties. Ginsenoside's antioxidant activity is correlated with its capacity to control the levels of glutathione, ROS-mediated NF-kB pathway, and regulation of the transit of iron and associated proteins, leading to diminished stored iron in the substantia nigra.

Vincamine, an alkaloid obtained from *Catharanthus roseus*, Family: Apocynaceae, has demonstrated antiparkinsonian activity through a variety of modes of action. It has a vasodilation function, which relaxes the muscles around the capillaries in neurons, improves glucose and other nutrients' flow in the brain, and increases ATP production via the Krebs cycle.

Baicalein, a flavonoid obtained from the Iranian plant (*Scutellaria baicalensis*, Family: Lamiaceae) roots, delays the synthesis of oligomers of α-Syn, reducing neurotoxicity and fibrillation.

11.4.3 NUTRACEUTICALS IN DEPRESSION

Mental depression, characterized by a downbeat or gloomy mood and diminished interest in social engagement, impairing routine, has a 15% frequency and a 7% yearly incidence. Research on the quality of food's impact on mood and brain health indicates that the nutrients derived from dietary goods are crucial for the healthy functioning of the human brain. There is growing evidence that folic acid and omega-3 fatty acids are also beneficial as monotherapies for unipolar depression, especially when used in conjunction with other treatments. A whole-grain diet high in nutrients can stimulate brain function and has demonstrably demonstrated results in the treatment of depression [30]. These nutrients include some vital macro- and micronutrients, minerals like zinc, vitamins like folic acid, and omega-3 fatty acids. The probable mechanisms of the antidepressant action of some nutraceuticals are shown in Figure 11.3.

11.4.4 NUTRACEUTICALS IN PSYCHOTIC DISORDERS

In addition to the functional roles that have been studied, nutritional supplements are crucial in the treatment of mood and psychotic disorders including schizophrenia and bipolar disorders [31]. Nutraceuticals significantly increase the therapeutic efficacy of the medications used and reduce the side effects by improving the efficiency of reuptake inhibition of monoamines

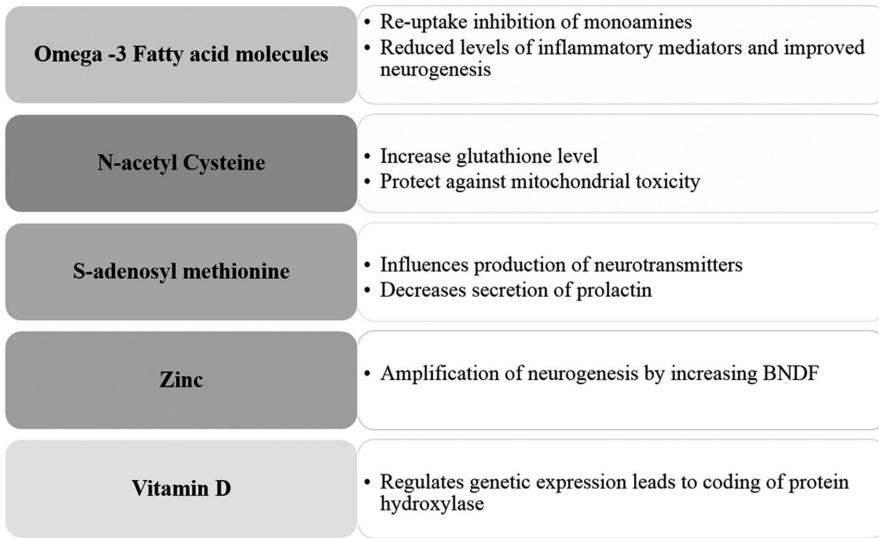
Omega -3 Fatty acid molecules
• Re-uptake inhibition of monoamines
• Reduced levels of inflammatory mediators and improved neurogenesis
N-acetyl Cysteine
• Increase glutathione level
• Protect against mitochondrial toxicity
S-adenosyl methionine
• Influences production of neurotransmitters
• Decreases secretion of prolactin
Zinc
• Amplification of neurogenesis by increasing BNDF
Vitamin D
• Regulates genetic expression leads to coding of protein hydroxylase

FIGURE 11.3 Probable mechanisms of antidepressant action.

[32–35]. Nutraceuticals, especially omega-3 fatty acids and vitamins such as vitamin D and folic acid, are commonly recommended for psychotic disorders.

Two main forms of polyunsaturated fatty acids, i.e., omega-3 and omega-6 series (e.g., alpha-linolenic acid and arachidonic acid, respectively), found in the human body are derived from docosahexaenoic acid (DHA), Eicosapentaenoic acid (EPA), and linoleic acid [36]. Each of them forms the phospholipid part of the cell membrane and is crucial for the human body. However, these need to be received via diet. Omega-3 EPA and DHA have characteristics at the molecular level that are relevant to psychotic illnesses and enhance dopaminergic and serotoninergic neurotransmission.

11.5 CHALLENGES WITH DRUG DELIVERY OF NEURO-NUTRACEUTICALS

Neuro-nutraceuticals have many advantages such as fewer side effects and cost-effectiveness over synthetic drugs used for neurological diseases, but their delivery is a challenging task due to poor absorption, low bioavailability, low solubility, and low permeability across the blood-brain barrier [37, 38]. The poor absorption rate is due to the lipophilic nature and low solubility

of the bioactive agent [39]. The bioavailability of bioactive compounds is hindered by poor solubility and permeability, as observed in the case of curcumin with issues like partial tissue distribution, first-pass metabolism, and a short half-life period. Larger molecules face challenges related to tissue permeability, P-glycoprotein efflux, and active transport. Additionally, interactions with other chemicals or drugs can disrupt therapeutic effects or lead to undesired outcomes. These factors collectively impact the therapeutic efficacy of nutraceuticals, necessitating exploration of methods to enhance their bioavailability and targeted delivery. Nano-formulations are employed to encapsulate nutraceuticals, addressing solubility and stability issues and facilitating their passage across the blood-brain barrier. Selection of encapsulating materials becomes crucial, considering that synthetic components used in pharmaceutical formulations may not be suitable for nutraceuticals. In the context of neuro-nutraceuticals, various nano-formulations have been researched to overcome delivery challenges.

11.6 RECENT ADVANCES IN DRUG DELIVERY OF NEURO-NUTRACEUTICALS

A perfect delivery system should be practically viable and release its bound contents when triggered through specific stimuli including enzymes, moisture, pH, temperature, and protecting them from other factors [43]. The development of the delivery system takes into account the physicochemical characteristics of nutraceuticals, including their solubility, chemical interactions, stability, amount needed in the finished product, and release mechanism [44]. Several nanotechnological efforts to encapsulate natural compounds, especially nutraceuticals, have been made. Both hydrophilic and lipophilic compounds can be incorporated in nano-formulation for boosting their synergistic impact [45]. Lipids, polymeric micelles, and proteins are used to incorporate the nutraceuticals instead of synthetic components, which are generally used for delivery systems as these have potential negative effects. The physicochemical characteristics of any substance need to be encapsulated, the intended target(s), and the application type determine the selection of the type of method of drug delivery as well as its ingredients [46]. It is essential to study primary nano-carriers employed for encapsulating the nutraceuticals.

Based on the components used for encapsulation, the delivery system for nutraceuticals can be divided into two groups: (i) lipid and surfactant-based

carriers, which include liposomes, solid lipid particles, nanostructured lipid carriers, niosomes, and self-dispersing lipid formulations; and (ii) biopolymer-based carriers, such as polysaccharide and protein-based carriers.

11.6.1 LIPOSOMES

Liposomes are phospholipid bilayer vesicular systems containing one (uni-lamellar) or several (multi-lamellar) concentric phospholipid membranes enclosing an aqueous core [47, 48]. The liposomal proficiency of possessing both water and lipid-soluble (in the aqueous core area and the lamellae, respectively) bioactive compounds is their key advantage in application [49]. Liposomes are ideal carriers of medicinal compounds, such as neuro-nutraceuticals, due to their biodegradable and biocompatible compositions. Various studies have been performed for the formulation of nutraceuticals for their better physiological stability and effective delivery.

Quercetin was encapsulated with cyclodextrin-coated liposomes, which had a greater encapsulation capacity and enhanced physicochemical qualities. A flavonoid called quercetin is well-known for its positive effects, which include anti-obesity, anti-cancer, anti-inflammatory, antioxidant, and AD progression prevention abilities. However, the main disadvantages of its targeted distribution are its weak chemical stability and water solubility. Quercetin has limited bioavailability and a short biological half-life due to its poor water solubility. According to the scientists, after 12 months of storage (at 4°C), the quercetin-loaded liposomes remained stable (assessed through particle size and quercetin concentration). Surprisingly, cyclodextrin-coated liposomes preserved more quercetin (98%) after 12 months [50].

Tan et al. prepared liposomes for carotenoids to improve their bio-accessibility as it is a challenge for their therapeutic effects. The carotenoids included in the research are β-carotene, lycopene, lutein, and canthaxanthin. The physical stability of liposomes, bio-accessibility, and release were investigated in simulated gastric fluid. The bio-accessibility is improved in the order: lutein > β-carotene > lycopene > canthaxanthin [51].

11.6.2 SOLID LIPID NANOPARTICLES (SLNS)

Submicron emulsions known as SLNs are created by homogenizing two immiscible phases with an amphiphilic surfactant present. These SLNs make it easier to keep the liquid phase present throughout the procedure. To achieve greater encapsulation efficiency, a slower rate of degradation,

and flexibility in content release profile, the lipid phase is melted at a high temperature [52]. Lipids like fatty acids, paraffin, triacylglycerol, glycerides, and waxes are generally preferred in SLNs preparations. The SLNs represent several advantages such as good stability, controlled and targeted release, good biodegradability and biocompatibility, high loading capacity, and low cost. Nutraceuticals can be incorporated into SLNs with the following different models:

1. **Solid Solution Model:** Nutraceuticals are molecularly dispersed in the lipid matrix in the solid solution model. By using a cold homogenization method, a solid solution model is prepared without adding a solubilizing surfactant. The SLNs showed controlled release properties that are based on dissolution mechanisms [53].
2. **Bioactive-Enriched Shell Model:** For the preparation of SLNs, the hot homogenization approach is used. This model can be utilized to achieve a burst release of nutrients, even if it might not be appropriate for a protracted release. An outer shell that is rich in nutraceuticals encloses the lipid core. Phase separation occurs during cooling, causing the lipid to precipitate first and solidify into a lipid core. The concentration of nutraceutical in the outer shell of the SLN is the result of the nutraceutical's re-partitioning into the remaining liquid phase [53].
3. **Bioactive-Enriched Core Model:** For preparation of SLNs, nutraceutical dissolves in the melted lipid at or near its saturation. When the melted lipid containing the nutraceutical is cooled, the supersaturation of nutraceuticals in the lipid causes the nutraceutical to precipitate before the lipid. The lipid contents around the central core enriched with nutraceuticals will get precipitated with more cooling as a membrane. This situation encourages a controlled discharge governed by Fick's diffusion law [53].

In a recent study, the physicochemical stability of carotene was significantly improved by encapsulating it within solid lipid nanoparticles (SLNs) containing palmitic acid, maize oil, and whey protein isolate (WPI). The presence of palmitic acid crystals formed a protective shell around the surface of the oil droplets, effectively shielding the encapsulated carotene. WPI played a crucial role in enhancing the oxidative stability of β-carotene, while the combination of maize oil and palmitic acid synergistically reduced the risk of carotene being excluded from the solid matrix and reaching the SLNs' surface.

This innovative system exhibited exceptional stability even under challenging conditions [54].

11.6.3 NIOSOMES

Niosomes, the vesicular structures, contain non-ionic surfactants such as polyoxyethylene alkyl ethers or esters [55] and can incorporate both water and lipid-soluble drugs. The advantages such as biodegradability, compatibility with biological systems, low cost, and stability make them an effective delivery system. Some nutraceuticals are encapsulated into niosomes for their better efficacy and stability. Ganesh et al. encapsulated lycopene into niosomes to enhance stability and then converted it into a gel for topical formulation. The prepared formulation was stable at 40±5°C for 90 days [56]. Murugesan et al. encapsulated quercetin and resveratrol into niosomes to improve bioavailability. The niosomes were prepared using a thin film hydration technique with cholesterol and span as non-ionic surfactants. *In vitro* and *ex vivo* studies showed a significant increase in bioavailability [57]. From the above-discussed studies, it may be concluded that nutraceuticals can be incorporated into niosomes to improve their bioavailability and stability.

11.6.4 NANOSTRUCTURED LIPID CARRIERS (NLCS)

In NLCs, the lipid phase is made up of a mix of liquid and solid lipids at room temperature. The main benefits of this system include better encapsulation efficiency, stability, controlled release, low toxicity, biodegradability, and bioavailability. This system was largely created to address SLN's shortcomings [57, 58]. These appealing qualities have attracted attention to NLCs over the past several years.

Quercetin, employed in the treatment of neurological disorders, faces limitations due to its chemical instability and inadequate aqueous solubility, restricting its broader applications. By using a high-pressure homogenization technique, quercetin and linseed oil are added to NLC to increase their solubility and stability. The co-loaded nanoparticles of quercetin and linseed oil were spherical, less than 100 nm in diameter. It was discovered that nano-encapsulated quercetin was delivered in NLC as an encapsulated amorphous form with less organized lipid cores. Additionally, at least 1,300 times more quercetin was soluble in hydrophilic matrices made of linseed oil and surfactants. *In-vitro* antioxidant activities and stability of quercetin NLC were also improved by the addition of linseed oil and the sustained release was obtained [59].

Pezeshki et al. [61] reported β-carotene-loaded NLC and investigated the particle size, percentage encapsulation efficiency, and stability. The various formulations were prepared by using different surfactant concentrations (1, 2, 3, and 4% w/v) and solid: liquid lipid ratios (2:1, 4:1, and 10:1). The formulation containing 2% surfactant concentration and solid: liquid lipid ratio of 10:1 was optimized. The optimal formulation had an entrapment efficiency of 97.7% and was stable for 14 days at 25°C [60].

To increase Co-enzyme Q10's water solubility and photo-stability, Wang et al. prepared co-enzyme Q10 (Co Q10) NLC. Co Q10's photo-stability was significantly enhanced when incorporated in NLC; more than 80% of it remained intact after one month of exposure to natural light. Co Q10-NLC provided a respectable high level of protection. After five months of exposure to natural light, 65% of Co Q10 remained in the NLC system. When compared to Co Q10 alone, the Co Q10 in the NLC-based formulation demonstrated significantly improved photo-stability and superior Co Q10 protection. The outcomes provided new insights into Co Q10's photo stability [61].

11.6.5 SELF-DISPERSING LIPID FORMULATIONS (SDLFS)

In self-emulsifying drug delivery systems (SEDDS), a combination of oils, surfactants, co-surfactants, and co-solvents is formulated into isotropic solutions. These systems, initially not emulsions, transform into emulsions upon contact with water or biological fluids [62, 63]. This technique enhances the solubility of nutraceuticals in the gastrointestinal tract, improving their absorption. Common oils, such as mono-glycerides, exhibit various self-assembling structures upon contact with water.

In a study using quercetin, encapsulation in a SEDDS composed of capmul MCM, Tween 20, and ethanol resulted in stable emulsions with favorable characteristics. The system maintained robustness and stability over time, passing various tests without exhibiting phase separation or turbidity for up to 6 months. Comparatively, the SEDDS with quercetin demonstrated comparable antioxidant activity to free quercetin, indicating the persistence of quercetin's characteristics in the presence of SEDDS components [1]. Similarly, Coenzyme Q10 was encapsulated in a solid SEDDS to enhance photo-stability and oral bioavailability, showing increased dissolution and a five-fold increase in bioavailability compared to a solution of solid SEDDS [65]. The solid SEDDS exhibited reduced photo reactivity, making it a promising formulation for improved drug delivery. Some nano-formulations based on lipid carrier systems, as mentioned above, are described in Table 11.2.

TABLE 11.2 Some Nanoformulations of Neuronutraceuticals

Designed Nano-Formulation	Nutraceutical(s)	Ingredient/ Formulation Challenges	Novel Drug Delivery System-Mediated Efficacy	References
Liposomes	Quercetin	Stability	Improved stability	[50]
	Lutin, β-carotene, lycopene, canthaxanthin.	Low bio-accessibility.	Improved bio-accessibility in the order: lutin> β-carotene> lycopene>canthaxanthin.	[51]
Solid lipid nanoparticle	Carotene	Stability	Improved stability	[54]
Niosomes	Lycopene	Stability	Improved stability	[56]
	Quercetin and resveratrol	Low bioavailability	Enhanced bioavailability	[57]
Nanostructured lipid carrier	Quercetin and linseed oil	Poor solubility in hydrophilic matrices and chemical instability.	Solubility is improved by 1,300 and stable for more than 3 months at 25°C.	[59]
	β-carotene	Lipophilic nature and low bioavailability in the crystalline form, highly reactive and sensitive to heat, light, and oxygen.	Entrapment efficiency and stability is significantly improved.	[60]
	Co-enzyme Q10	Solubility, photo-stability.	Solubility and photo-stability of co-enzyme Q10 is significantly improved.	[61]
Self-dispersing lipid formulation	Quercetin	Stability and susceptibility to oxidation.	Improved stability and protected antioxidant property.	[1]
	Co-enzyme Q 10	Photostability and low bioavailability.	Improved bioavailability and photosensitivity.	[65]

11.6.6 BIOPOLYMER-BASED DELIVERY SYSTEM

Biopolymers such as polysaccharides and proteins can be used for nutraceutical delivery. Polysaccharides are long chains of branched/unbranched chains of sugar moieties joined through glycosidic bonds. These can be obtained from natural sources such as animals, plants, bacteria, and algae [66]. Nutraceuticals can be encapsulated in polysaccharides as they have unique properties such as similarity with the human extracellular matrix

[67], involved in biological processes such as immune recognition and cell signaling. These can be easily degraded in the body by enzymatic or hydrolytic reactions and cleared by the immune system [68]. Numerous nano-formulations utilizing polysaccharides have been developed to address challenges in delivering nutraceuticals, including β-carotene, epigallocatechin, and omega-3 fatty acids. This approach aims to overcome issues associated with nutraceutical delivery.

The bioactive compounds can be incorporated into proteins as the exterior surface possesses functional groups that have the ability to encapsulate hydrophilic and lipophilic bioactive constituents. These compounds are biocompatible, non-toxic, biodegradable, sustainable, and inexpensive [69]. Caseins, due to their ability to form micelles, and whey protein, due to physiochemical and functional properties such as amphiphilic nature and denaturation, are used for the delivery of nutraceuticals. The nutraceuticals encapsulated in biopolymer-based drug delivery systems are listed in Table 11.3.

Pan et al. prepared a biopolymer-based delivery system for β-carotene to improve solubility in an aqueous solution. The biopolymer was prepared with casein and dextran using a Maillard reaction, making it soluble in an aqueous solution. This prepared polymer was used to encapsulate the β-carotene, which helps improve solubility and stability in aqueous dispersion and under light exposure. The formulation will release the bioactive constituent through pepsin or trypsin hydrolysis. The results showed that the prepared formulations can be used for hydrophobic and photosensitive bioactive compounds [70].

Nano-liposomes for epigallocatechin-3-gallate (EGCG) were prepared with N, N-dimethyl hexadecyl carboxymethyl chitosan (DCMC) and dextran sulfate as biopolymer-based delivery system using film evaporation method for improving the EGCG stability as it is sensitive to oxidation [71] and chemically unstable, leading to low bioavailability. *In-vitro* release, encapsulation efficiency, and stability studies were performed with these nanoliposomes. The results of these studies showed the prepared formulations possess high encapsulation efficiency, sustained release, and strong protective capability [72].

Patel et al. prepared biopolymeric particles using Zein and Sodium caseinate to improve bioavailability, aqueous solubility, and provide protection against degradation in alkaline pH. Zein obtained from corn (*Zea mays*, Family: Poaceae) is a hydrophobic protein used for the preparation of colloidal particles due to its amphiphilicity-based self-assembly [73, 74]. Quercetin-loaded biopolymeric colloidal particles were synthesized through the precipitation of quercetin and zein, achieved by introducing their hydroalcoholic solution into an aqueous solution with sodium caseinate serving as

an electrostatic stabilizer. The antioxidant study confirmed that the quercetin encapsulated in colloidal particles provides chemical stability in alkaline pH as well as against light [75]. Some biopolymer-based drug delivery systems for neuro nutraceuticals are briefly described in Table 11.3.

TABLE 11.3 Some Biopolymer-based Drug Delivery System for Neuronutraceuticals

Biopolymers	Formulation	Nutraceuticals	Ingredient/ Formulation Challenges	Novel Drug Delivery System-Assisted Efficacy	References
Casein-graft-dextran	Nanoparticles	β-Carotene	Low solubility, stability against oxidation.	After nano-formulation of β-carotene with casein-graft-dextran, stability against oxidation was significantly improved.	[70]
Dextran sulfate-amphiphilic chitosan derivative	Nano-liposomes	Epigallocatechin gallate	Susceptible to oxidation	Protected from oxidation, Improved encapsulation efficiency, sustained release obtained.	[72]
Zein, sodium caseinate	Polymeric micelles	Quercetin	Photostability and stability in alkaline solution.	Enhanced photostability and increased stability in alkaline solutions are achieved through the encapsulation of a substance within sodium caseinate protein.	[73]

11.7 CLINICAL OUTCOMES

Neurological disorders such as AD, mental depression, PD, schizophrenia, etc., are seriously jeopardizing public health and affecting the quality of life. In clinical practice, various synthetic drugs prescribed for managing the aforementioned neurodegenerative diseases need prolonged administration, which causes severe side effects such as sedation, altered motor functions, restlessness, disturbed sleep patterns, mental confusion, mood swings, on-and-off states of mind, affected behavior, etc. To overcome such chronic adverse effects that worsen the quality of life, the general public as well as health professionals are turning towards alternative systems of medicines and/or therapies in which herbal drugs play a vital role. Nowadays, neuro nutraceuticals, especially those comprising herbal constituents, are gaining attention for managing neurological disorders. A plethora of clinical studies

is in the pipeline to investigate the insight of nutraceuticals for neurodegeneration and other psychological disorders. The clinical studies on some nutraceuticals for neurological disorders are briefly described in Table 11.4.

TABLE 11.4 Outcomes of Clinical Studies of Some Nutraceuticals Used in Neurological Disorders

Diseases	Nutraceuticals	Model	Effect/Study	References
Alzheimer's disease	Saffron (*Crocus sativus*), 30 mg/day.	Phase 2 double-blind clinical trial in mild- to moderate Alzheimer's disease patients.	Saffron (*Crocus sativus*) was well-tolerated and lessened the severity of the symptoms.	[76]
	2.152-mg docosahexaenoic acid every day for 6 months.	33 individuals	On treatment with docosahexaenoic acid, a 28% increase in CSF DHA and a 43% increase in CSF EPA; Increased CSF EPA was three times larger in nonAPOE4 carriers than in APOE4 carriers; there was no change in brain volume or cognitive scores.	[77]
Parkinson's disease	Coenzyme Q10	Pilot study on PD subjects	CoQ10 doses positively correlated with activities of CI, II, and III slowed down nigrostriatal degeneration.	[78]
	–	Placebo-controlled randomized clinical trial in early PD subjects.	Improved quality of life rather than motor function in the high-dose group.	[79]
Depression	Vitamin D_3 (50,000 I.U.) for 3 months	62 patients (male and female with MDD and randomized groups.	After taking vitamin D supplements for three months, female patients showed the greatest improvement in their depression symptoms. Among males with severe depression diagnoses showed a statistically significant improvement in their BDI ratings ($p < 0.05$). Other biochemical measures did not significantly differ between the two groups. These results imply that vitamin D supplementation may, through a serotonin-dependent mechanism, lessen symptoms of Major Depressive Disorder (MDD), especially in females.	[80]

TABLE 11.4 *(Continued)*

Diseases	Nutraceuticals	Model	Effect/Study	References
–	Tryptophan 2–4 g/day along with fluoxetine for 8 weeks.	A randomized, double-blind, placebo-controlled trial with 30 individuals with major depressive disorder.	Daily administration of Fluoxetine (20 mg) and tryptophan (2 g) together at the outset of treatment for MDD appears to be a safe protocol and showed rapid antidepressant and a better protective effect on slow-wave sleep.	[64]

11.8 CONCLUSION

Nowadays, various studies have been performed with nutraceuticals in the prevention and treatment of chronic diseases including neurological disorders. Nutraceuticals have neuroprotective, antioxidant, and anti-inflammatory properties, which enhance neuroprotective protein synthesis by targeting ligands and receptors. Nutraceuticals have created newer opportunities for affordable and effective management of neurodegenerative disorders because synthetic drugs have serious side effects. There are many challenges in the delivery of nutraceuticals such as low solubility, low bioavailability, low stability, and poor penetration of the BBB. Nutraceuticals can be combined with nano-formulations to overcome the above-discussed challenges. Various delivery systems based on lipids such as liposome-mediated delivery systems, solid lipid nanoparticles, nanostructured lipid carriers, etc., have been discussed to eradicate limitations in the delivery of nutraceuticals and make them suitable for the prevention of neurological disorders.

KEYWORDS

- **Alzheimer's disease**
- **liposome**
- **nanoparticles**
- **neuro-degeneration**
- **neurological disorders**
- **neuro-nutraceuticals**
- **Parkinson's disease**
- **solid lipid nanoparticles**

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